THE ROLE OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT AS AN ANTIMICROBIAL PROPHYLAXIS STRATEGY IN PAEDIATRIC INTENSIVE CARE

Thesis submitted in accordance with the requirements of the

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by

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GLOSSARY

AH	Alder Hey
AB	Antibiotic
AGNB	Aerobic Gram-negative bacilli
AML	Acute myeloid leukaemia
APACHE	Acute physiology and chronic health evaluation
BMT	Bone marrow transplant
CI	Confidence Interval
Diag	Diagnostic Samples
ESBL	Extended Spectrum Beta-Lactamases
GCS	Glasgow Coma Score
GOSH	Great Ormond Street Hospital
ICP	Intra-cranial pressure
ICU	Intensive Care Unit
IPI	Intrinsic Patogenicity Index
IL	Interleukin
IQR	Interquartile range
MRSA	Methicillin-resistant Staphylococcus aureus
OR	Odds Ratio

PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PIM	Paediatric Index of Mortality
PPM	Potential Pathogenic Micro-organisms
PTA	Polymyxin/Tobramycin/Amphotericin
QDS	Four times daily
RCT	Randomised controlled trial
RR	Relative Risk
SAP	Single-drug antifungal prophylaxis
SDD	Selective Decontamination of the Digestive Tract
SMR	Standardised Mortality Rate
SOD	Selective Decontamination of the Oropharynx
Surv	Surveillance Samples
TDS	Three times daily
TNF	Tumour necrosis factor
VAP	Ventilator associated pneumonia
VISA	Staphylococcus aureus with intermediate sensitivity to vancomycin
VRE	Vancomycin-resistant enterococci

Summary

THE ROLE OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT AS AN ANTIMICROBIAL PROPHYLAXIS STRATEGY IN PAEDIATRIC INTENSIVE CARE

A. J. Petros

The object of this thesis is to explore whether there may be any benefit in using selective decontamination of the digestive tract (SDD) in critically ill children who require treatment in an intensive care unit (ICU).

There is a significant body of work that confirms unequivocally that SDD reduces morbidity and mortality in adults. This comprises of 64 RCT and 11 meta analyses, which demonstrate significant reductions in morbidity and mortality without resistance emerging.

Chapter 1 describes and defines the components and application of SDD. Chapter 2 puts SDD into context with other therapies used in ICU to reduce mortality. The evidence supporting SDD is categorised in terms of GRADE scoring and compares other interventions on the same scale. SDD is the only manoeuvre that has the highest recommendation. Chapter 3 describes the 11 meta analyses of the 64 RCTs in detail. Chapter 4 describes a meta analysis of the four paediatric RCTs available in the literature. The results demonstrate that mortality is not affected by SDD. However, there is a reduction in pneumonia rates in children even with the small numbers available to analyse.

Chapter 5 looks at the national database for children admitted to PICUs for the 5 year period 2004-2008 and describes demographics for the group and looks in detail at the causes of admission at Alder Hey (AH) children's hospital and Great Ormond Street Hospital and nationally. AH was reviewed as this centre practiced SDD during the entire period and for a number of years prior to 2004. Great Ormond Street

Hospital is the largest PICU in the country and both are compared to the national database. Finally, Chapter 6 compares the mortality rates between the three groups and looks in more depth at the severity of illness of the various groups to see if SDD has any effect on different subsets of patients.

From the data available no real differences were found between the hospitals. It is perhaps not surprising that there is no significant difference between the groups as a result of one unit using SDD. It is difficult to imagine that one manoeuvre can impact on such a heterogeneous yet small group. To provide randomized controlled trial (RCT) evidence that SDD is superior sample size is very important in these circumstances. A sample size of 30,000 children would be needed. This would require 100% recruitment for two years from every PICU in the UK. Hence, surrogate measures and inferences have to be relied upon.

Chapter 1

BASICS OF ANTIMICROBIAL PROPHYLAXIS OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT

In 1975 Frantz et al reported the clinical course of 54 neonates with necrotizing enterocolitis (NEC) compared to a matched group of 98 control patients. On the day of life that NEC occurred, all 54 NEC patients and 63% of controls were receiving standard formula feedings, both at 80cal/kg/day. Stool cultures at the time revealed a significantly increased growth of *Klebsiella* species in NEC neonates compared to control patients. The authors suggested that the combined presence of certain intestinal bacteria and enteric feedings, perhaps requiring a background of mucosal ischemia, may be of aetiologic significance in the development of NEC and its radiologic hallmark, pneumatosis intestinalis.

The concept of intestinal translocation of enteric bacteria and its association with Gram-negative sepsis was established in animal models in 1979 by Berg. The term translocation was originally used by Berg and Owens to refer to the passage of viable bacteria from the gut through the epithelium to the lamina propria and thence to mesenteric lymph nodes and possibly other organs (Berg RD) and subsequently modified by Alexander to refer to the movement of viable and nonviable microbes or their toxic products across an intact intestinal barrier (Alexander JW).

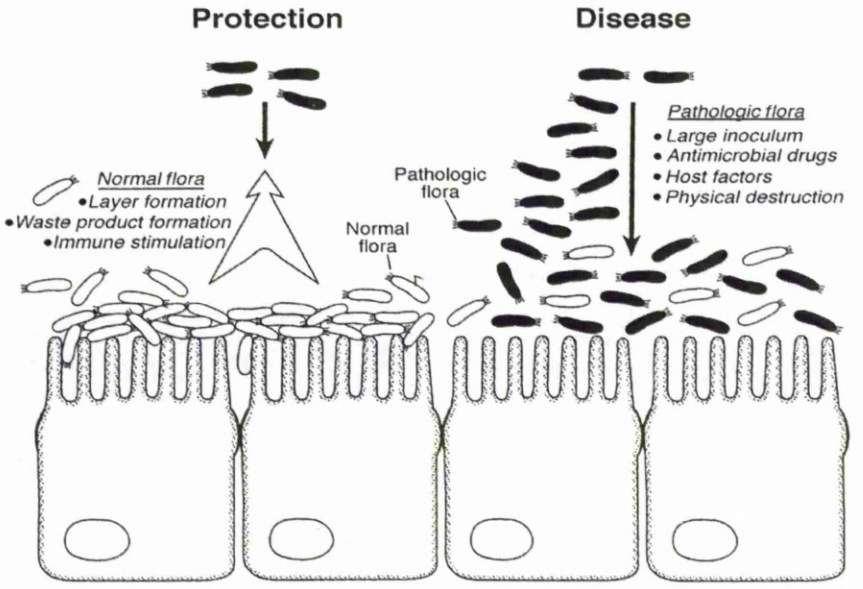
One fundamental premise of SDD is that gut bacterial overgrowth is harmful to the critically ill patient (Figure 1.1).

1. Overgrowth in the oropharynx causes lower airway infections as potential pathogens spill over into the lungs and in the gut bacteria migrate and translocate across the permeable gut wall.

2. Overgrowth also induces immunosuppression.

Figure 1.1

Diagram depicting the normal and abnormal carrier state within the lumen of the gut and the mechanisms by which normal flora compete with gut pathogens. In illness, bacterial overgrowth occurs and bacteria translocate through the mucosal membranes.



The intestinal normal flora can enhance host defense by occupying the gut in large numbers and diversity, thereby *1*) preventing colonisation of the host by pathogens by more successfully competing for essential nutrients or for epithelial attachment sites; *2*) producing antimicrobial compounds, volatile fatty acids, and modified bile acids that in turn create a luminal microenvironment unfavorable for the growth of pathogens; and *3*) inducing recruitment of immune cells and activation of appropriate immune and inflammatory responses. Bacterial overgrowth overcomes these micro-environmental and immunologic responses and disrupts the integrity of the epithelial defense by normal flora. Adapted from Davis CP (Lei L).

3. Aerobic Gram-negative bacilli (AGNB) carried in the gut translocate from the lumen of the gut into the Peyers patches where their endotoxin component stimulates macrophages to produce cytokines such as tumour necrosis factor (TNF). Cytokinaemia results in a down regulation of macrophage activity in the gut, liver, abdomen and lungs (Deitch EA) and is almost certainly responsible for the inflammation of organs resulting in multiple organ failure (Waydhas C).

4. Finally, gut overgrowth guarantees increased spontaneous mutation, polyclonality and subsequent antimicrobial resistance (van Saene HKF (2008 *CDT*)).

These four harmful consequences of gut overgrowth can be reduced by SDD (de la Cal MA 2005; van Saene JJM; Horton JW; Conraads VM) as it controls overgrowth and thereby reduces the faecal endotoxin pool (van Saene JJM).

The Philosophy of SDD: Control of Overgrowth

The major hazard for any intensive care patient is the development of infection. Prevention of such a complication is the absolute essential of intensive care. Selective decontamination of the digestive tract is a strategy aimed at preventing infection using prophylactic parenteral and enteral antimicrobials. It is a prophylactic antimicrobial regimen specifically designed to prevent severe endogenous and exogenous infections of lower airways and blood in the critically ill patients requiring treatment on the intensive care unit and produces a significant reduction in mortality in this vulnerable group (Silvestri L (2009)). It is based upon two fundamental principles (van Saene HKF (1996 *JHI*)):

Firstly, that pathogenesis of infection is due to a limited range of potential pathogens. There are six normal potential pathogens: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Escherichia coli and Candida albicans*. Abnormal flora consists of nine abnormal potential pathogens, eight aerobic Gram-negative bacilli and methicillin-resistant *Staphylococcus aureus* (MRSA). The eight AGNB are *Klebsiella, Proteus, Morganella, Citrobacter, Enterobacter, Serratia, Acinetobacter* and *Pseudomonas species*. (Figure 1.2)

Secondly, the three types of pathogenic pathways each require a different intervention. The SDD concept defines three different types of infection (Table 1.1).

Table 1.1

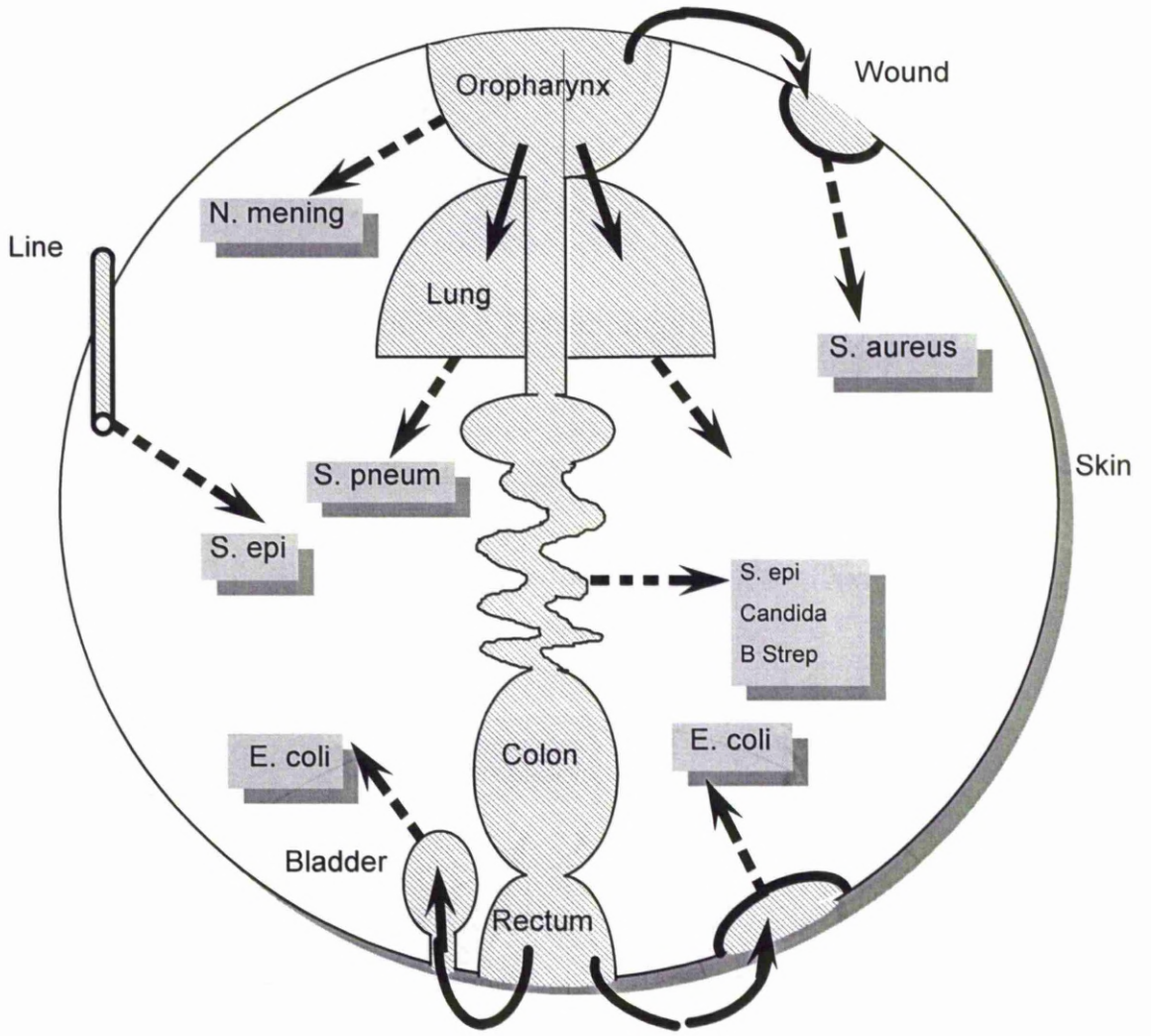
Philosophy of SDD - Carriage classification of infections. PPM – potential pathogenic micro-organisms,

Infection	PPM	Timing	Frequency	Manoeuvre
Primary endogenous	6 'normal' 9' abnormal'	<1 week	55%	Parenteral antimicrobials
Secondary endogenous	9 'abnormal'	>1 week	30%	Hygiene and enteral antimicrobials
Exogenous	9 'abnormal'	Anytime during ICU treatment	15%	Hygiene and topical antimicrobials

1) Primary endogenous – which generally develops within a week and is the most frequent type of infection responsible for approximately 55% of infections. This type of infection is caused by potential pathogens, which are present in the admission (oropharynx or gut) flora and may be either normal or abnormal flora.
2) Secondary endogenous infection – which is invariably caused by abnormal bacteria not present in the admission flora but acquired during treatment on the ICU. This type of infection generally occurs after one week and represents 30% of infections.
3) Exogenous infection is caused by abnormal potential pathogens never carried in the digestive tract but introduced directly in the patient from an external source. Exogenous infection may occur at any time, during ICU treatment, and accounts for 15% of infections (Silvestri L (2009)).

Figure 1.2

Pathogenesis of infection is due to a limited range of potential pathogens. The figure describes the potential routes of entry of these pathogens.



Prevention of the primary endogenous route requires an initial course of parenteral antimicrobials which will eradicate carriage of normal flora and should the patient already be infected, also treat that infection. Cefotaxime was originally chosen for two reasons: its spectrum of activity against normal flora and the majority of the AGNB (Stoutenbeek CP (1987)), secondly, it is highly effective in eradicating oropharyngeal and gut carriage of normal flora due to high salivary and biliary concentrations (Stoutenbeek CP (1989)). Yeast carriage cannot be eradicated using parenteral antifungals, only enteral polyenes, including amphotericin B and nystatin, have been shown to achieve this (van Saene HKF *ICM* 2003).

To prevent secondary endogenous infection enteral antimicrobials polymyxin and tobramycin are administered to prevent the acquisition of abnormal flora in the carrier state and eradicate it should the patient be carrying abnormal flora. Secondary endogenous infection may occur if enteral antimicrobials are administered too late and should be treated via the parenteral route.

The combination of enteral polymyxin (Hoeprich PD) and tobramycin (Neu HC) was chosen because it covers all abnormal AGNB, including *Pseudomonas* species. Additionally, there is a synergistic combination between the two (Kuipers JS). Only in the case of MRSA endemicity is enteral vancomycin added to polymyxin/tobramycin to eradicate and clear the MRSA carrier state (Silvestri L (2002)).

Standard hygiene measures and scrupulous attention to sterile technique are crucial in preventing the introduction of potential pathogens from external sources directly into sterile organs, bypassing the carrier state. Identical antimicrobials polymyxin, tobramycin and vancomycin are indicated for topical use, e.g. in a paste on a tracheostomy site to control exogenous lower airway infections. These three interventions were first combined by Stoutenbeek in 1984 (Stoutenbeek CP (1984)). Stoutenbeek developed the prophylactic strategy further to include surveillance cultures thus creating the full four component SDD prophylaxis (Figure 1.2).

Mechanisms of action in controlling overgrowth

The acceptance of the classification of the carrier state is crucial in explaining the efficacy of SDD in order to select the correct antimicrobials (Silvestri L (2009) *Chest*). Carriage may be either high grade (defined as $\geq 10^5$ potential pathogens per mL or gram of digestive tract secretions) or low grade (defined as $<10^5$ potential pathogens per mL or gram of digestive tract secretions) (van Saene HKF (1996 *JHI*)). The continuing success of SDD is based on the chosen antimicrobials ability to clear carriage, in particular high grade carriage also known as gut overgrowth(Husebye H).

In order for the target micro-organisms to be completely eradicated, the concentrations of the selected antimicrobials in saliva, bile and faeces must be effective (Novick WJ Jr; Maier H; Gotoff SP; Bodey GP; Tedesco F; Geraci JE; Currie BP; Hofstra W; Hofstra W 1982). These concentrations are shown in Table 1.2 and are deemed to be of greater importance than sparing the colonisation resistance flora (van der Waaij D).

Table 1.2

Effective concentrations against prevailing micro-organisms achieved in saliva, bile and faeces with antimicrobials used in SDD regimen given enterally. These concentrations are more important than sparing of the colonisation resistance flora (van der Waaij D; Vollaard EJ).

Antimicrobials selected for SDD	Concentrations (mg/L) in		
	Saliva	Bile	Faeces
Cefotaxime	6	20	
Polymyxin E			16-1,000
Tobramycin			100
Amphotericin B			60
or Nystatin			<100
Vancomycin			3,000-24,000

Practical guidelines on how to use SDD

All patients who require treatment on the ICU for minimally two days require the immediate administration of parenteral cefotaxime in high doses for four days, to control mortality due to 'early' primary endogenous infections caused by the 'normal' potential pathogens such as *S.pneumoniae* and *S.aureus* (Table 1.3). Additionally, high doses of parenteral cefotaxime eradicate oropharyngeal and gut carriage of normal potential pathogens such as *S.aureus* and *E.coli*. The enteral antimicrobials are given throughout the treatment on ICU to control mortality associated with 'late' secondary endogenous infections. A paste or gel is applied into the lower cheeks to prevent and, if already present, eradicate oral carriage of 'abnormal' PPM, i.e. to decontaminate the oropharynx. A suspension is administered via the nasogastric tube to decontaminate stomach and gut. Polymyxin and tobramycin with or without vancomycin are used to control 'abnormal' carriage of AGNB, in particular *Pseudomonas aeruginosa*. In case of MRSA endemicity, enteral vancomycin is added to polymyxin/tobramycin. Tobramycin is replaced by paromomycin in case of endemicity of AGNB producing extended spectrum beta-lactamase (ESBL) resistant to tobramycin. In case of *Serratia* endemicity, both polymyxin and tobramycin are replaced by paromomycin. Enteral amphotericin B or nystatin is used to control yeast overgrowth. The third component is topical antimicrobials to control exogenous infections. Finally, regular surveillance samples of throat and rectum are obtained to monitor efficacy and safety of SDD.

Efficacy of the SDD regimen

There are now 64 RCTs (Abdel-Razek SM; Abele-Horn M; Aerdts SJ; Arnow PM; Barret JP; Bergmans DC; Bion JF; Blair P; Boland JP; Bouter H; Brun-Buisson C ; Camus C; Cerra FB; Cockerill FR 3rd; de Jonge E; de la Cal MA (2005); de Smet AM; Diephenhrst GM; Farran L ; Ferrer M; Finch RG; Flaherty J; Gastinne H; Gaussorgues PH ; Georges B ; Gosney M; Hammond JM; Hellinger WC; Jacobs S; Kerver AJ; Korinek AM; Krueger WA; Laggner AN; Lingnau W; Luiten EJ; Martinez-Pellús AE; Martinez-Pellús AE (1997); Oudhuis GJ; Palomar M; Pneumatikos I; Pugin J; Quinio B; Rayes N; Rios F; Rocha LA; Rodríguez-Roldán JM; Rolando N; Rolando N (1996); Ruza F; Sánchez García M; Schardey HM; Smith SD; Stoutenbeek CP (1996); Stoutenbeek CP (2007); Tetteroo GW; Ulrich C; Unertl K; Verwaest C; Wiener J; Winter R; Yilmazlar A; Yu J; Zobel G; Zwaveling JH) using SDD.

There are eleven meta-analyses examining only RCTs assessing the efficacy of SDD (Vandenbroucke-Grauls CMJ; D'Amico R; Safdar N; Liberati A; Silvestri L (2005 *ICM*); Silvestri L (2007 *JHI*); Silvestri L (2008 AIC); Silvestri L (2009 JCC); Liberati A (2009 *Cochrane*); Silvestri L (2010); Silvestri L (2010 Resp Med)) (Table 1.4). Five meta-analyses have the endpoint of lower airway infection (Vandenbroucke-Grauls CMJ; D'Amico R; Liberati A; Silvestri L (2008); Liberati A (2009)) and all show a significant reduction of lower airway infections due to both Gram-negative and Gram-positive bacteria (OR 0.28, 90%CI 0.22-0.38).

The most recent meta-analysis also demonstrates that SDD using parenteral and enteral antimicrobials reduces multiple organ failure dysfunction syndrome (MODS) (Silvestri L (2010)). In that study the sample size of 1270 patients was too small to show a survival benefit.

Mortality was the endpoint in eight meta-analyses (Vandenbroucke-Grauls CMJ; D'Amico R; Safdar N; Liberati A; Silvestri L (2007 JCI); Silvestri L (JCC); Liberati A (2009 Cochrane); Silvestri L (2010)), five had sample sizes between 4,902 and 8,065 where a survival benefit is consistently shown (D'Amico R; Liberati A (2004); Silvestri L (2007 JCI); Silvestri L (2009 JCC); Silvestri L (2010 CCM)). Mortality reduction was not significant in the remaining three meta analyses due to the small sample size (259, 491 and 1270 patients). Survival benefit is almost certainly due to the control of severe infections of both lower airways and blood. Bloodstream infections due to AGNB were significantly reduced (OR 0.36; CI 95% 0.22 -.0.60) (Silvestri L (2007 JHI)), fungaemia was also reduced (OR 0.89; CI 95% 0.16-4.95) but this did not achieve significance (Silvestri L (2005 ICM)). Although Gram-positive blood stream infections increased, this was not significant (OR 1.03; CI 95% 0.75-1.41) (Silvestri L (2008 AIC)). Figure 1.3 demonstrates the incidence of publications of RCTs and meta-analyses over the last 24 years. There was a flurry of RCTs in the 1990s and then the number of meta-analyses increased being able to draw upon data from the RCTs.

Table 1.3 Full four component-strategy of SDD.

Target PPM and antimicrobials	Total daily dose (4 x daily)		
	<5 years	5 – 12 years	>12 years
1. parenteral antimicrobials: 'normal' PPM cefotaxime (mg)	150/Kg	200/Kg	4000
2. enteral antimicrobials: 'abnormal' PPM A. oropharynx AGNB : polymyxin E with tobramycin MRSA : vancomycin Yeasts : amphotericin B or nystatin	2 g of 2% paste or gel 2 g of 4% paste or gel 2 g of 2% paste or gel		
B. gut AGNB : polymyxin E (mg) with tobramycin (mg) MRSA : vancomycin (mg) Yeasts : amphotericin B (mg) or nystatin (units)	100 80 20-40/Kg 500 2×10^6	200 160 20-40/Kg 1000 4×10^6	400 320 500-2000 2000 8×10^6
3. topical antimicrobials: 'abnormal' PPM	2% polymyxin E with tobramycin and 4% vancomycin paste or gel on tracheostoma, wound		
4. surveillance cultures of throat and rectum on admission, Monday, Thursday	'Abnormal' PPM in overgrowth concentrations		

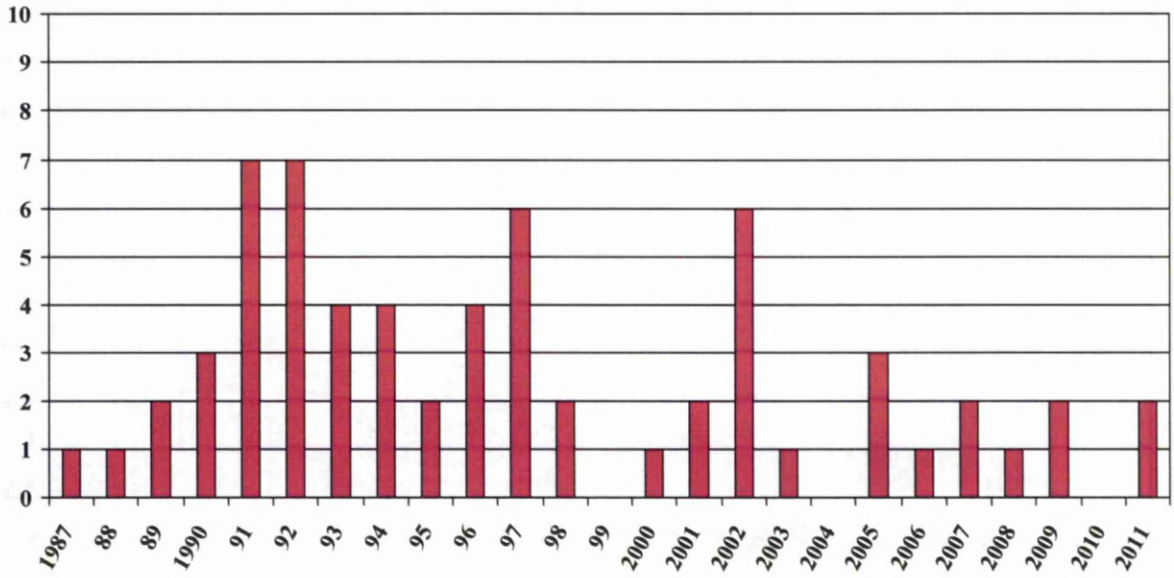
Table 1.4 The 11 meta-analyses of the 64 RCTs look at the efficacy of SDD.

Author	No RCTs	Sample Size	Lower airway infection OR (95%CI)	Bloodstream infection OR (95%CI)	Multiple Organ Dysfunction Syndrome OR (95%CI)	Mortality OR (95%CI)
Vandenbroucke-Grauls	6	491	0.12, 0.08 t o 0.19	NR		0.92, 0.45 to 1.84
D'Amico	33	5727	0.35, 0.29 to 0.41	NR		0.80, 0.69 to 0.93
Safdar	4	259	NR	NR		0.82, 0.22 to 2.45
Liberati	36	6922	0.35 0.29 to 0.41	NR		0.78 0.68 to 0.96
Silvestri yeasts	42	6075	NR	0.89, 0.16 to 4.95		NR
Silvestri	51	8065	NR	0.63, 0.46 to 0.87		0.74, 0.61 to 0.91
Silvestri G-ve G+ve	54	9473	 0.07, 0.04 to 0.13 0.52, 0.34 to 0.78	 0.36, 0.22 to 0.60 1.03, 0.75 to 1.41		 NR NR
Silvestri	21	4902	NR	NR		0.71, 0.61 to 0.82
Liberati	36	6914	0.28, 0.20 to 0.38	NR		0.75, 0.65 to 0.87
Silvestri	7	1270	NR	NR	0.50 0.34 to 0.74	0.82 0.51 to 1.32
Silvestri	12	2252	0.54 0.42 to 0.69	NR		NR

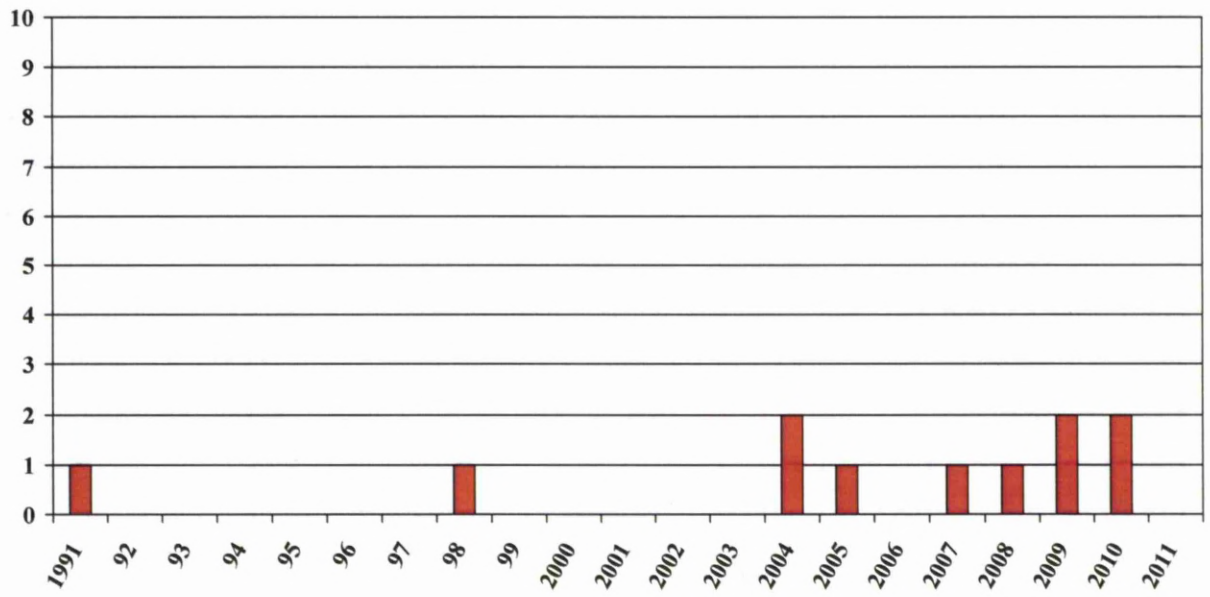
Figure 1.3

Incidence of publications of randomized controlled trials and meta-analyses on SDD.

64 randomized controlled trials (RCT) on SDD over 24 years (1987-2011)



11 Meta-analyses of SDD over 21 years (1991-2011)



Safety profile of the SDD regimen

Concerns about resistance are legitimate for any antimicrobial prophylaxis (Kaiser AB; Petros A) and the safety of SDD relies on resistance not emerging against the SDD antimicrobials (Baxby D). A recent meta-analysis of the 64 SDD RCTs does not show any increase in resistance to the SDD antimicrobials but a significant reduction in resistance.

The main resistance problems in ICU come under four categories

1. AGNB: in particular *Klebsiella* species, can produce extend ESBL. *Acinetobacter* and *Pseudomonas* species are often multi-resistant to different classes of antimicrobials, principally due to reduced permeability of these two bacteria (Jarlier V).
2. MRSA: which differs from country to country and can be endemic in the ICU and eradication poses serious problems for the intensivist (Bronzwaer SL).
3. Azole-resistant Candida species: is an increasing problem on the ICU since the introduction of fluconazole (Lyon GM).
4. Vancomycin-resistant enterococci (VRE): is a greater problem in North America than in Europe (Zhanel GG).

The SDD regimen and resistant organisms

Resistant Aerobic Gram Negative Bacilli

There are 3 RCTs with the endpoint of antimicrobial resistance amongst AGNB (Brun-Buisson C; de Jonge E; de Smet AM). In a Parisian hospital there was endemicity of an ESBL producing *Klebsiella*. The carriage and infection rates in the control group were 19.6% and 9%, respectively; enteral antimicrobials were added and the rates were reduced to 1% and 0% (Brun-Buisson C). A Dutch study demonstrated that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin and polymyxins occurred in 16% of SDD patients compared to 26% of control patients with a relative risk (RR) of 0.6 (95% CI 0.5 – 0.8) (de Jonge E). The most extensive RCT (6,000 patients) was also undertaken in The Netherlands. This study demonstrated that the percentage of patients carrying AGNB resistant to ceftazidime was significantly less in those receiving enteral polymyxin/tobramycin compared to standard care (de Smet AM) (Table 1.5).

Table 1.5

ICU Patients carrying aerobic Gram-negative bacilli (AGNB) resistant to ceftazidime receiving selective decontamination of the digestive tract (SDD) versus standard care (de Smet AM). Figures are percentages of patients

AGNB	SDD	Standard Care	
E.coli	1.3	3.3	$p<0.05$
K.pneumoniae	0.4	2.2	$p<0.05$
E.cloacae	1.7	4.7	$p<0.05$
P.aeruginosa	0.7	2.6	$p<0.05$

The Gut Concept

The gut concept may explain the findings of these three RCTs in that there is significantly less resistance when enteral antimicrobials are added. Parenteral antimicrobials alone do not reach lethal concentrations within the gut when excreted via bile, resulting in faecal overgrowth of AGNB which in turn promotes resistant mutant strains. The addition of enteral antimicrobials clears overgrowth (high grade carriage) including resistant mutants.

Approximately 30% of patients either import, acquire or develop *de novo* antimicrobial resistance (Viviani M; Garrouste-Orgeas M). The common denominator for these three mechanisms is the gut. ICU patients are susceptible to gut overgrowth due to impaired gut motility and they have a high risk for *de novo* development (van Saene HKF (2008 *CDT*)). The polymyxin/tobramycin combination creates a unique environment. This mixture is synergistic and results in very high bactericidal levels in both saliva and faeces which maintains colonisation resistance (Mulder JG; van Saene HKF(1998)). These three features of SDD when combined eradicate overgrowth and profoundly influence the balance of forces associated with resistance (Silvestri L(2001)).

Practically all ESBL-producing AGNB are sensitive to the enteral combination of polymyxin/tobramycin (Taylor ME). Although rare, some ESBL-producing AGNB such as *Klebsiella* species may be resistant to tobramycin (Al Naiemi N). Under these circumstances, the eradication of this type of abnormal carriage has been unsuccessful using polymyxin/tobramycin. The reason for this being that a combination of two enteral agents active against the abnormal ESBL-producing AGNB is required for successful SDD (Brun-Buisson C (1991)). Tobramycin needs to be replaced by an active aminoglycoside, e.g. neomycin (Brun-Buisson C (1989)) or paromomycin (Abecasis F, Bodey GP). Parenteral antimicrobials that disregard the patient's gut ecology may promote acquisition, carriage and subsequent overgrowth of ESBL-producing AGNB (Hoyen CK; Pultz NJ; Martins IS). Therefore blind administration of SDD is not advocated and surveillance of faecal flora is required with modification of the enteral component of SDD as necessary.

There are four long-term studies (≥2 years) evaluating the impact of polymyxin/tobramcyin on resistance amongst AGNB (Stoutenbeek CP (1987 JAC); Leone M; Sarginson RE; Heininger A) (Table 1.6). The resistance data of the long term studies confirm the RCT findings that rates of carriage and infection due to resistant AGNB in patients receiving parenteral and enteral antimicrobials are not increased but are actually lower compared with patients receiving solely parenteral antimicrobials.

Resistant MRSA

SDD was not originally designed to cover MRSA, as it was not a significant problem in the early 1980's. During 7 of the 64 SDD RCTs MRSA was endemic in study units, resulting in a trend towards higher infection rates in those 7 RCTs (de la Cal MA 2004; Ferrer M; Gastinne H; Hammond JM; Lingnau W; Verwaest C; Wiener J). In order to combat endemic MRSA enteral vancomycin needs to be added to SDD (Silvestri L (2002)).

Three studies using long term SDD with enteral vancomycin (≥2 years) did not report any emergence of *Staphylococcus aureus* with intermediate sensitivity to vancomycin (VISA) or vancomycin-resistant enterococci (VRE) (de la Cal MA (2004

Table 1.6 Long term studies of enteral polymyxin/tobramycin resistance.

Author	Study		Patients		% patients with carriage (surv) and/or infection (diag) due to resistant AGNB
	Type	Period	Type	Number	
Stoutenbeek	Prospective observational	2½ years	Trauma	164	4% of patients carried *E.coli* resist to tobra *Acinetobacter* resist to tobra *Pseudomonas* resist to tobra
Leone	Retrospective case-control	6 years	MV	720	No difference between test and control
Sarginson	Prospective observational	4 years	Children ≥4 days of ventilation	1241	4% of children were infected with resistant bacteria including MRSA
Heininger	Prospective observational	5 years	MV >2 days	1913	0.05% of patients infected with *E.coli* resist to tobramycin

Surv = Surveillance samples; Diag = diagnostic samples MV = mechanical ventilation

JHI); Cerdá E; Viviani M) (Table 1.7). Similarly, MRSA overgrowth is invariably present in the critically ill when MRSA is endemic and guarantees the presence of VISA strains following the parenteral use of vancomycin (Guerin F). The addition of enteral vancomycin produces faecal vancomycin levels of up to 3,000mg/L preventing or eradicating, if already present, the VISA mutants. A similar scenario applies to carriage and overgrowth of abnormal VRE and the intravenous administration of antimicrobials such as linezolid, resulting in the emergence of linezolid-resistant VRE mutants (Verma N). As far as we are aware, there are no studies that assessed the efficacy of enteral vancomycin in preventing and eradicating carriage and overgrowth of VRE (Stiefel U; Salgado CD).

Azole-resistant Candida species

The use of azoles, in particular, fluconazole, has been reported to increase *Candida krusei, Candida glabrata* and *Candida albicans* resistance (Lyon GM). Surveillance cultures of throat and rectum are essential in detecting carriers of *Candida* species resistant to fluconazole. Knowledge of carriage of resistant strains allows the enteral administration of polyenes such as amphotericin B or nystatin to eradicate the carrier state, preserving the value of fluconazole as a useful antifungal agent (van Saene HKF (1999 *JHI*)).

Vancomycin-resistant enterococci

VRE was endemic in the units where 2 of the 64 RCTs were performed (Arnow PM; Hellinger WC). Carriage and infection rates of VRE were similar in both test and control groups. Six RCTs added enteral vancomycin to the classical SDD regimen and screened for VRE (Bergmans DC; Gaussorgues PH; Korinek AM; Krueger WA; Pugin J; Schardey HM). VRE was not isolated from any samples either diagnostic or surveillance. Enteral vancomycin in high doses does not promote VRE rather, parenteral antimicrobials which disregard gut ecology are responsible for the promotion of VRE (Stiefel U; Salgado CD).

Table 1.7

Long term studies of enteral vancomycin on staphylococcal and enterococcal resistance.

Author	Study		Patients		% patients with carriage (surv) and/or infection (diagn) due to VISA and/or VRE
	Type	Period	Type	Number	
de la Cal	Prospective observational	4 years	Med/Surg >3 days of MV	799	13/799 (5%) carried VRE
Cerda	Prospective observational	4 years	Burns	375	No emergence of VRE or VISA in either surv or diag
Viviani	Prospective observational	2 years	MV >3days	265	No emergence of VRE or VISA in either surv or diag

Surv = Surveillance samples;
Diag = diagnostic samples;
VISA = vancomycin-intermediate *Staphylococcus aureus*;
VRE = vancomycin-resistant enterococci
MV = mechanical ventilation

SDD was introduced into AH paediatric intensive care unit in 1999 (Sarginson RE) and a database developed to record the relevant data on both carriage and infection (van Saene HKF (2005 2nd ed)). The density of patients carrying and infected with resistant bacteria did not increase over the 5 years use of SDD (Figures 1.4 and 1.5). Density of patients was defined as the number of patients carrying or infected with resistant bacteria per month of 100 days, i.e. number of patients per month divided by number of patient days per month multiplied by 100.

The over-riding message from RCTs, meta-analyses and long-term studies is that the addition of enteral to parenteral antimicrobials does not promotes resistance but contributes to its control (van Saene HKF (2003 ICM)).

Benchmarking SDD against other manoeuvres which reduce mortality on ICU

It is only now after 60 years of intensive care medicine that ICU manoeuvres are being properly assessed against the rigorous endpoint of reduction in mortality. This is perhaps not surprising, as the methods of grading success have only recently been described and evidence based medicine driven clinical practice established.

In recent years, there are five manoeuvres that have been shown to reduce mortality in RCTs: ventilation with low tidal volumes for acute lung injury and respiratory distress syndrome (ARDS Network 2000); recombinant human activated protein C for severe sepsis (Bernard GR); intensive insulin therapy (Van den Berghe G); low doses of steroids in patients with septic shock (Annane D) and SDD (de Jonge E, de Smet AM, Krueger WA) (Table 1.8). Table 1.8 reports the levels of evidence obtained using the Grade system (Atkins D; Dellinger R), which classifies the quality of evidence as high grade (Grade A), moderate (Grade B), low (Grade C) or very low (Grade D) (see Chapter 2). RCTs begin as high quality evidence but may be downgraded due to limitations in implementation, inconsistency or imprecision of the results, indirectness of the evidence, and possible reporting bias. An example of this is high glucose control (A down to C): the success of the original Belgian RCT (van den Berge G) in reducing mortality has not to date been reproduced (NICE-SUGAR, Beardsall K). Additionally, a recent tight glucose control meta-analysis produced negative and contradictory results (Wiener RS).

The Grade system also classifies recommendations as strong (Grade 1) or weak (Grade 2). The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. A strong recommendation in favour of an intervention reflects that the desirable effects of adherence to a recommendation (beneficial health outcomes, less burden on staff and patients and cost savings) will clearly outweigh the undesirable effects (harms, more burdens, greater costs).

SDD is the only evidence based manoeuvre with a Grade 1A recommendation.
All RCTs of SDD, whether mono (de Jonge E) or multicentre (de Smet AM; Krueger WA), that assessed the full four component SDD protocol consistently demonstrated a significant survival benefit, provided the sample size was large enough. Similarly,

all meta-analyses that assessed the full SDD protocol with a large enough sample size showed a consistent survival benefit (D'Amico R; Liberati A; Silvestri L (2007 *JHI*); Silvestri L (2009 (*JCC*); Liberati A (*Cochrane*)). The mortality data show an intriguing observation that trial design determines the magnitude of the survival benefit (Silvestri L (2009 (*JCC*)). The relative reduction in the odds ratio for mortality was 41% when all patients receive the full SDD protocol (de Jonge E), 29% when half the patients receive the antimicrobial prophylaxis (Silvestri L (2009 (*JCC*)) and 17% when one third of the population are treated with SDD (de Smet AM; Oostdijk EA). In the trial of the unit-wide application of SDD (de Jonge E), the SDD protocol virtually eliminated transmission of potential pathogens via the hands of care-givers and hence exogenous infection in decontaminated patients. Mixing decontaminated and non-decontaminated patients in the same unit dilutes the survival benefit. This is the case in the RCT design, wherein the patients receiving and not receiving SDD are treated within the same unit (de Jonge E). Patients who are decontaminated protect control patients from transmission, acquisition, carriage and subsequent infection, whereas the patients not receiving SDD remain at risk of acquiring potential pathogens and subsequent exogenous infections, resulting in a reduction in the true effect of SDD. The most recent multicentre RCT in 6,000 patients with a 17% relative reduction – albeit statistically significant – clearly underlines the issue of diluting the SDD effect by increasing the number of non-decontaminated patients treated in the same unit with patients receiving SDD (de Smet AM; Oostdijk EA).

Costs implication for using SDD

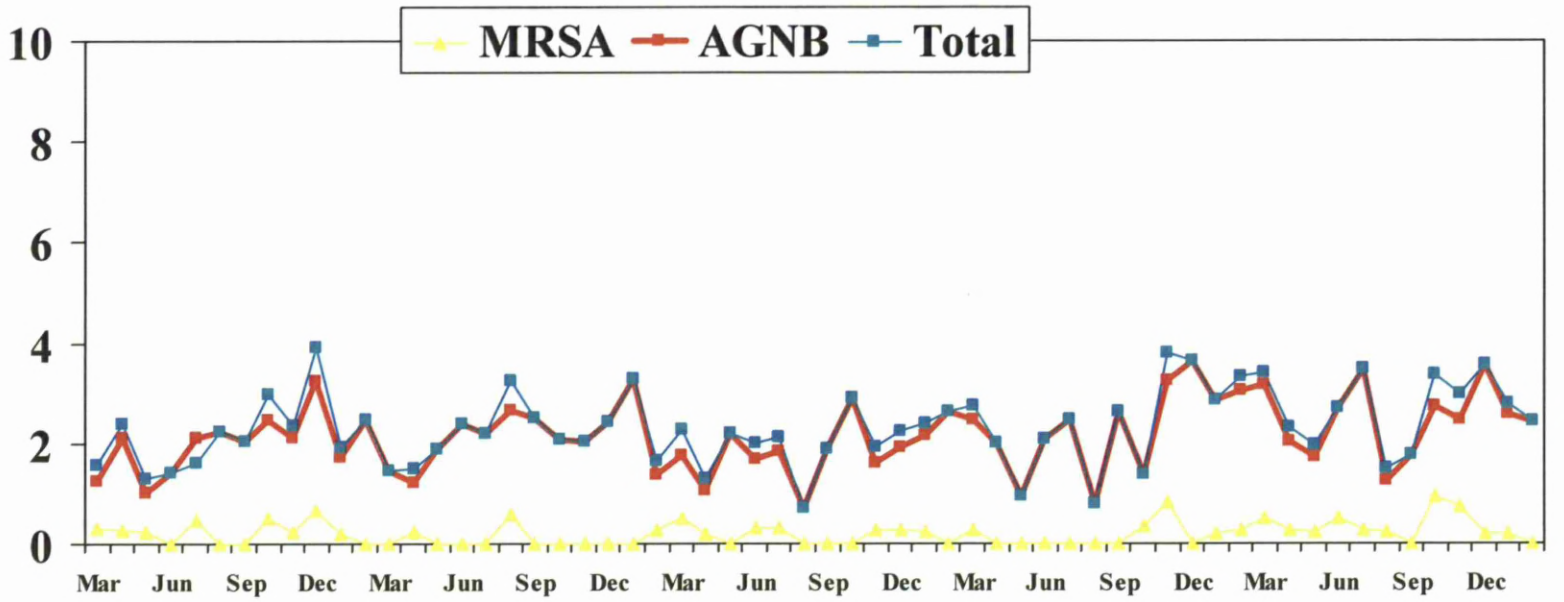
Although the cost effectiveness of SDD has not yet been formally calculated the daily costs of 6-12 Euros (de Smet AM; Quinio B; Collard HR) can hardly be an issue for an ICU intervention that reduces pneumonia, septicaemia and mortality by 72%, 37% and 29% respectively (Table 1.4).

Table 1.8

ICU-interventions that reduce mortality.

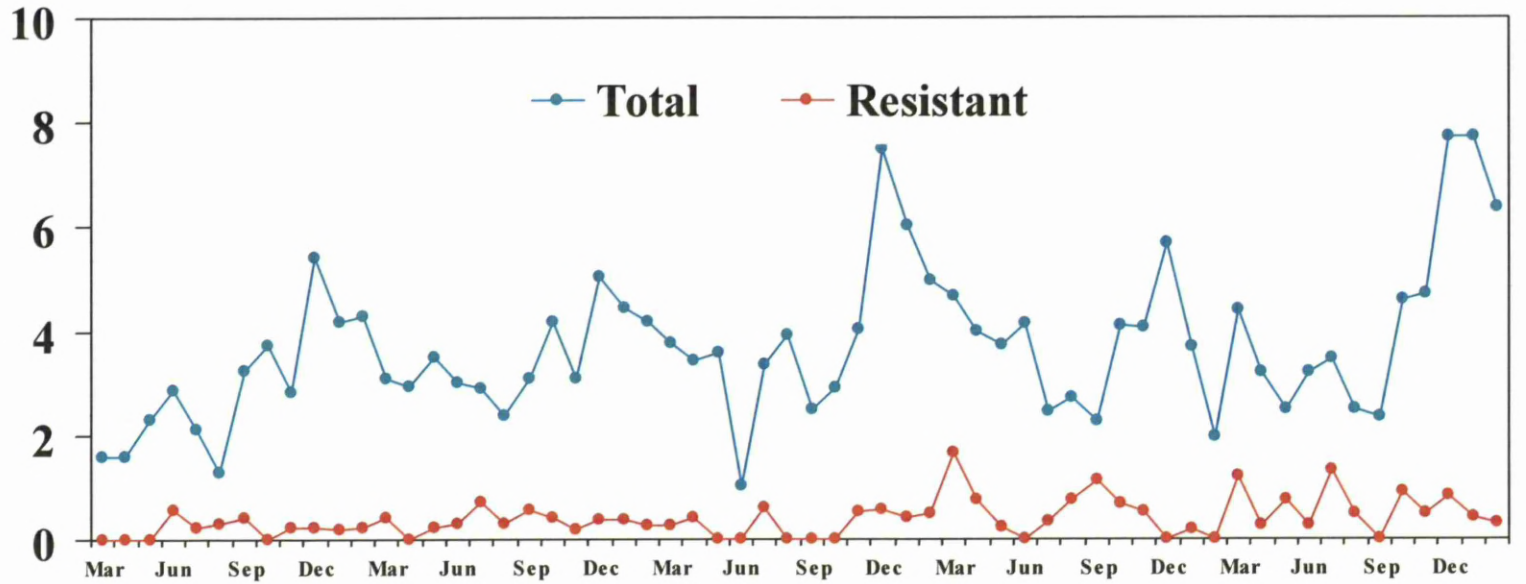
Intervention	Relative Risk (95% CI)	Absolute mortality reduction (%) (95% CI)	Number needed to treat	Grade of Recommendation
Low tidal volume (ARDS Network)	0.78 (0.65-0.93)	8.8 (2.4-15.3)	11	1B
Activated protein C (Bernard GR)	0.80 (0.69-0.94)	6.1 (1.9-0.4)	16	2B
Intensive insulin (Van den Berghe G)	0.44 (0.36-0.81)	3.7 (1.3-6.1)	27	2C
Steroids (Annane D)	0.90 (0.74-1.09)	6.4 (-4.8-7.6)	16	2C
SDD (de Jonge E, de Smet AM, Krueger WA)	0.65 (0.49-0.85)	8.1 (3.1-13.0)	12	1A

Figure 1.4 Density of patients carrying resistant bacteria 1999-2004. No significant resistance patterns emerged over the five years.



Number of patients carrying resistant micro-organisms per month of 100 patients days

Figure 1.5 Density of patients with infections due to number of resistant micro-organisms 1999-2004.



Total number of patients with infections due to resistant micro-organisms per month of 100 patient days.

Chapter 2

EVIDENCE-BASED MEDICINE IN INTENSIVE CARE

Introduction

In intensive care there have been many clinical trials evaluating numerous new therapies and much data generated. How is all this data to be evaluated and which specific treatment options should be chosen? This is where evidenced based medicine comes to the fore. It involves integrating clinical expertise, best research evidence and patient values. Clinical expertise involves the ability to use clinical skills and past experience to identify risks and benefits of potential interventions. Best research evidence includes relevant clinical research into accuracy and specificity of diagnostic tests and the power of the prediction of these tests, either science based or patient-centred.

Evidence based medicine (EMB) was extolled by David Seckett who described two processes, one for assessing the quality of a therapy on a scale of I to IV and a second for making recommendations for usage of that therapy on a scale of A-D. However, more recently a newer method of grading the quality of evidence and strength of recommendation for a new therapy has been developed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is being increasingly used as the structure on which to develop guidelines (Jaeschke R). The GRADE Working Group reported its suggestions in 2004 with further refinement in 2008 (Atkins D; Schünemann HJ). The use of a structured approach to collect, analyse and summarise all the relevant evidence allows the production of grades of recommendations.

The GRADE system is used widely by the World Health Organization, the American College of Physicians, the American Thoracic Society, the Cochrane Collaboration and many other organizations, up to 25 different groups demonstrating GRADE's success as a methodology (Guyatt GH).

GRADE guides the assessment of the quality of evidence for a particular treatment

or therapy. The study design, study quality, consistency, and directness are all assessed. The GRADE system classifies the quality of evidence in one of four levels—high (A), moderate (B), low (C) and very low (D). The factors influencing the decision on quality are described in Table 2.1. Evidence from randomized controlled trials (RCTs) contributes to high quality evidence, but confidence in the evidence may be decreased for several reasons; study limitations; inconsistency of results; indirectness of evidence; imprecision and reporting bias (Table 2.1).

Observational studies such as cohort and case-control studies start with a "low quality" rating. However, grading upwards may be possible if for example the size of the treatment effect is very large, if there is a strong causal relationship.

GRADE also makes recommendations from strong (1) to weak (2). The former is where the intervention clearly outweighs its undesirable effects and the latter where the trade-off between desirable and undesirable effects is less clear. As to making recommendations for a specific therapy this involves a balance between benefits and harms. Making a recommendation inevitably involves placing a relative value on each outcome though it is difficult to judge how much weight to give to different outcomes (Atkins D).

In making a recommendation four main factors should be considered (Table 2.2).

- The trade-offs –this should consider the estimated size of the effect for the main outcomes, the confidence limits around those estimates, and the relative values placed on each outcome.
- The quality of the evidence
- Translation of the evidence into specific practice, allowing for factors that could qualify the expected effect, such as proximity to a hospital or availability of necessary expertise
- Uncertainty about the baseline risk for the population of interest.

The strong or weak grading is felt to be of greater clinical important than classifying the quality of the intervention. Using GRADE provides a framework for structured assessment and can help to ensure that appropriate judgments are made about a new therapy or manoeuver.

Table 2.1

Descriptions of Levels and Quality used in the GRADE system.

Quality	Level	Description
High quality	A	Further research is very unlikely to change our confidence in the estimate of effect. Randomised control trials.
Moderate quality	B	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality	C	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Observational studies.
Very low quality	D	Any estimate of effect is very uncertain. Any other evidence.

Confidence in the quality of evidence used in GRADE

Decreases if:	
	Serious (- 1) or very serious (- 2) limitation to study quality
	Important inconsistency (- 1)
	Some (- 1) or major (- 2) uncertainty about directness
	Imprecise or sparse data (- 1)
	High probability of reporting bias (- 1)
Increases grade if:	
	Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
	Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
	Evidence of a dose response gradient (+1)
	All plausible confounders would have reduced the effect (+1)

Table 2.2

Factors influencing recommendations by GRADE.

Net benefits	the intervention clearly does more good than harm.
Trade-offs	there are important trade-offs between the benefits and harms.
Uncertain trade-offs	it is not clear whether the intervention does more good than harm.
No net benefits	the intervention clearly does not do more good than harm.

The ICU literature was searched using these GRADE rules for manoeuvres that may impact on infectious morbidity and mortality. We have classified the most common manoeuvres according to levels of evidence and grades of recommendations (Table 2.3).

Infection control manoeuvres

Hand washing, isolation, protective clothing, care of equipment and environment

It has never been shown in a RCT that hand hygiene prevents pneumonia and reduces mortality in ventilated patients. The efficacy of hand hygiene on the incidence of infection has been studied in 8 non-randomized studies (Casewell M; Massanari RM; Maki DG; Simmons B; Doebbeling RN; Webster J; Koss WG; Slota M) (Table 2.4). Data about the incidence of pneumonia are not presented in these studies. The only study that demonstrated an impact on mortality due to hand hygiene is the cohort study of Semmelweis in 1861 in post-partum women reducing mortality due to puerperal sepsis from 11% down to 3% (Silvestri L *JHI* 2005).

There are no data available on the effect of isolation, protective clothing, care of equipment and environment on the pneumonia rate and mortality in ventilated patients (Cepeda JA).

Table 2.3

Analysis of the literature and grading of evidence, and recommendations for the control of morbidity and mortality due to infection in ventilated patients on ICU.

	Reduced infection		Reduced Mortality	
	Level of evidence	Grade of recommendation	Level of evidence	Grade of recommendation
Non antibiotic interventions Hand washing/isolation/ protective clothing/ care of equipment and environment	D	2	D	2
Positioning				
Rotation therapy	None	None	None	None
Semi-recumbent position	None	None	None	None
Subglottic secretion drainage	None	None	None	None
Oral antiseptic decontamination	None	None	None	None
Immunomodulation				
• Immunonutrition	A	1	None	None
• Steroids	None	None	B	1
• Immunoglobulins	None	None	C	2
• Activated protein-C	None	None	B	1
• Anti-inflammatory modulators	None	None	A	1
Antibiotic interventions Selective Decontamination of the Digestive tract (SDD) (4 component)	A	1	A	1

These five traditional infection control measures target the control of transmission of micro-organism via hands of carriers. They are important but the impact should not be overestimated. An optimal infection control policy can only reduce infections due to micro-organisms acquired on the unit i.e. secondary endogenous and exogenous infections. They fail to influence primary endogenous infections due to micro-organism present in the admission flora. This type of infection is the major infection problem on the ICU varying between 60-85%.

Non antibiotic interventions

Positional Therapy

Severely ill patients who require ventilation are almost always treated in the supine position. This leads to collapse of the lower parts of the lung and reduced clearance of lower airway secretions. These two factors increase the risk of pneumonia. Treating a patient in a specialised rotating bed in which the patient is continuously rotated from -40° to +40° around their longitudinal axis could theoretically help in the prevention of pneumonia.

There is one meta-analysis available of 6 RCTs and also a further two RCTs (Choi SC; Summer WR; Traver GA). A significant reduction in pneumonia was found in patients who received rotational therapy. Of the 6 studies, 5 were performed in surgical or neurological patients. The sixth trial in which there was no reduction in pneumonia was performed in non-surgical ICU patients and a more recent RCT in a mixed ICU population does not support the meta-analysis. Rotation therapy requires special beds, is associated with considerable costs and is unpleasant for the patients. A cost effective analysis is not available.

Semi-recumbent position

Although in general the throat has been considered as the internal source of potential pathogenic micro-organisms (PPM) causing pneumonia, it is suggested that aspiration of PPM carried in the stomach may play a role in the pathogenesis of pneumonia, the so called stomach-lung route (Craven DE). Based upon this concept, ventilating patients in a semi-recumbent position is thought to have a beneficial effect on reducing the incidence of reflux and aspiration from the stomach whereby

Table 2.4

Studies into the effect of hand hygiene on the incidence of nosocomial infections including pneumonia.

Author	Year	Study Design	N	Outcome: infectious morbidity	Evidence
Casewell	1977	Sequential	Not mentioned	Significant reduction in nosocomial infections during Klebsiella outbreak Effect on pneumonia not mentioned	2D
Massanari	1984	Cross-over	5859	Significant reduction of nosocomial infection on some ICUs. Effect on pneumonia not mentioned	2A
Maki	1989	Cross-over	Not mentioned	Significant reduction of nosocomial infection on some ICUs. Effect on pneumonia not mentioned	2B
Simmons	1990	Historically controlled	Not mentioned	No effect	2D
Doebbeling	1992	Cross-over	1894	Significant reduction of nosocomial infection on some ICUs. No effect on pneumonia	2A
Webster	1994	Sequential	Not mentioned	Control of MRSA outbreak. Significant reduction of nosocomial infections	2D
Koss	2001	Prospective, randomized	153	No effect on pneumonia	2A
Slota	2001	Prospective, randomized	98	No effect on pneumonia	2A
Cepeda	2005	Prospective	Not mentioned	No effect on cross infection	2B

pneumonia in ventilated patients could be prevented. This manoeuvre has been investigated in three randomized control trials (Drakulovic MB; van Nieuwenhoven CA; Keeley L) (Table 2.5). The first study shows that ventilating patients in a semi-recumbent position leads to a significant reduction in pneumonia. Mortality rates however, were identical in both test and control group. Patients who underwent abdominal or neurosurgery and patients with refractory shock and patients who were readmitted to ICU within one month were excluded. The second RCT failed to confirm these results; there was no difference in pneumonia rate or mortality. The treatment of ventilated ICU patients in semi-recumbent position at an angle of 45° is difficult in practice and is often associated with frequent changes in patient position. Recently, Keeley was also unable to demonstrate any reduction in ventilator associated pneumonia in patients nursed at 45 ° ($p<0.176$). Meta analysis of these studies reveals no significant impact on VAP by this manoeuver. Cost is not reported as an issue for this intervention (Silvestri L *JCC* 2010; Alexion 2009).

Continuous aspiration of sub- glottic secretions

Stasis of saliva contaminated with potential pathogens above the cuff on the endotracheal tube increases the risk of aspiration pneumonia. The removal and prevention of this salivary stasis using continuous aspiration via a specially designed endotracheal tube is thought to prevent pneumonia. The intervention of subglottic secretion drainage (SSD) has been evaluated in 10 RCTs (Mahul P; Valles J; Kollef MH; Smulders K; Metz C; Bo H; Liu SH; Lorente L; Zheng RQ; Bouza E). Three studies were performed in a mixed ICU population requiring ventilation for >72hr and a fourth study in cardiac surgery patients. The results of these trials are not consistent. Two studies showed a significant reduction in pneumonia the other two failed to show any impact on pneumonia during ventilation. There was no difference in mortality in test and control group in any of the studies; although the specially designed tubes and suction equipment are expensive this technique has been suggested to be cost effective on theoretical grounds only. There were no harmful side effects associated with this manoeuvre in any of the studies. Bo et al found that the presence of subglottic secretion may be an origin of the pathogenetic organisms of ventilator associated pneumonias (VAP) (Bo H). The morbidity of VAP in mechanically ventilated patients can be reduced by SSD. Liu et al confirmed that

migration of the dominant bacteria of the subglottic secretion was one of the important factors for ventilator associated lower airway infection. The concentration of bacteria in the subglottic secretion was significantly reduced by subglottic secretion drainage when SSD was used and that SSD reduced the incidence of ventilator associated airway infection and VAP in patients ventilated of <5d (Liu SH). Zheng supported these conclusions (Zheng RQ). However, Lorente et al found that the use of an endotracheal tube with polyurethane cuff and subglottic secretion drainage helps prevent early- and late-onset VAP (Lorente L). Bouza et al demonstrated that continuous aspiration of subglottic secretions reduces the incidence of VAP in patients who are at risk (Bouza E).

There are two meta analyses. Dezfulian reported on 5 RCTs involving 896 patients. They found that SSD reduced the incidence of ventilator-associated pneumonia by nearly 50% (RR=0.51; 0.37-0.71), by reducing early-onset pneumonia occurring within 5-7 days after intubation. SSD also shortened the duration of mechanical ventilation by 2 days and the length of stay in the ICU by 3 days and delayed the onset of pneumonia by 6.8 days. Dezfulian et al concluded that SSD appears effective in preventing early-onset ventilator-associated pneumonia among patients expected to require >72 hours of mechanical ventilation (Dezfulian C). Silvestri et al (the 21st Anesthesia and ICU Symposium 2008) reported on 10 RCTs of SSD (Table 2.5), 9 of which reported results on pneumonia rates. In 1953 patients studied, there was a 57% reduction in VAP (OR 0.43, 95% CI 0.32-0.58; p<0.001) and in 1846 patients in 7 of the 9 RCTs who reported, there was no effect on mortality. So subglottic drainage is effective in preventing VAP; though sub group analysis revealed it was not effective in cardiac surgery patients.

Oropharyngeal Decontamination using Antiseptics

There are now 16 RCTs, which report varying degrees of success of oropharyngeal decontamination using antiseptics (De Riso AJII; Fourrier F; Houston S; MacNaughton PD; Grap MJ; Fourrier F; Segers P; Koeman M; Bopp M; Tad YD; Tantipong H; Panchabhai TS; Scannapieco FA; Munro CL; Bellissimo-Rodrigues F; Cabov T). However, the outcome of six meta-analyses confirms that antiseptic usage

Table 2.5 Randomized controlled trials and meta-analyses into the effect of non-antibiotic interventions on the pneumonia rate and mortality in ventilated patients. RCT=randomized controlled trial; MA=meta-analysis; SR=Systematic Review; RR=relative risk (95% confidence intervals)

Manoeuvre	Author	Year	Study Design	n	Pneumonia	Mortality	GRADE
Rotation therapy	Choi	1992	MA 6 studies	419	RR 0.50 p=0.002	No difference	2A
	Traver	1995	RCT	103	RR 0.62 p=0.21	RR 0.62 p=0.21	2A
Semi-recumbent position	Silvestri	2010	MA 3 studies	337	OR, 0.59 (0.15-2.35) (p=0.45)	OR 0.86 (0.54-1.37) (p=0.53)	1A
	Van Saene	2009	MA 2 studies	311	OR 0.56 (0.06-5.54)	OR 0.81 (0.47-1.41)	1A
Subglottic suction drainage	Dezfoulian	2005	MA 5 studies	896	RR 0.5 (0.35- 0.71) (p<0.001)	Not significant	1A
	Silvestri L	2008	MA 9 studies	1953	OR 0.43 (0.32-0.58) (p<0.001)	OR 0.93 (0.71-1.21) (p=0.57)	1A
	Van Saene	2009	MA 7 studies	1178	OR 0.40 (0.28-0.56)	OR 0.99 (0.71-1.38)	1A
Oropharyngeal decontamination using antiseptics	Pineda	2006	MA 4 studies	1202	OR 0.42 (0.16-1.06)	OR 0.77 (0.28-2.11)	1A
	Chlebicki	2007	MA 7 studies	1650	RR 0.70 (0.47-1.04) (p=0.83)	RR 1.07 (0.76-1.51) (p=0.69)	1A
	Chan	2007	MA 7 studies	2144	RR 0.56 (0.39 to 0.81)	RR 0.96 (0.69 to 1.33)	1A
	Kola	2007	MA 7 studies		RR 0.58 (0.45-0.74)	Not significant	1A
	Van Saene	2009	MA 11 studies	2752	OR 0.49 (0.35-0.67)	OR 0.98 (0.64-1.50)	1A
	Carvajal	2010	MA 10 studies		OR 0.56 (0.44-0.73)	Not significant	1A

has no benefit in reducing pneumonia or mortality (Pineda LA; Chlebicki MP; Chan EY; Kola A; van Saene HKF JCC 2009; Carvajal C) (Table 2.5). In 1202 patients Pineda et al reported that use of oral decontamination with chlorhexidine did not result in significant reduction in the incidence of nosocomial pneumonia in patients who received mechanical ventilation, nor altered the mortality rate. Chlebicki et al demonstrated no mortality benefit with chlorhexidine, though in seven small RCTs there was a reduction in VAP most marked in cardiac surgery patients. Neither antiseptic nor antibiotic oral decontamination reduced mortality or duration of mechanical ventilation or stay in the intensive care unit in a meta-analysis of 11 studies by Chan et al. Kola et al found in seven RCTs a reduction in the relative risk (RR) of lower respiratory tract infections in those receiving chlorhexidine (RR (random): 0.58). However, these results only applied to patients ventilated for up to 48h. From 10 studies but not all RCT Carvajal et al report a reduction in the risk of VAP with chlorhexidine (OR: 0.56, 95% CI: 0.44-0.73). However, neither a reduction in mortality, nor lengths of MV nor ICU length of stay were seen.

Immunomodulation

Enteral feeding

Total parenteral nutrition (TPN) has been shown to be harmful in terms of infection rates and liver impairments. This prompted the desire to enterally feed the ICU patient as quickly as possible because it is thought to be essential for the gut anatomy and physiology in order to prevent loss of mucosa integrity and subsequent translocation. In addition several nutrients added to the enteral feed have been shown to influence immunologic and inflammatory responses in humans. There are two meta-analyses available on immunonutrition in the critically ill (Beale RJ; Heyland DK) (Table 2.6). Both meta analyses demonstrated a significant reduction in overall infection rate, though they do not specifically say pneumonia, there was no reduction in mortality in either of the meta-analyses. Surgical patients seemed to benefit more than medical patients. In two large RCTs mortality rate was significantly higher in the subgroup who received immunonutrition. Some have speculated that added arginine may have been detrimental to the immune system.

Table 2.6

Randomized controlled trials into the effect of non-antibiotic interventions (immunonutrition and steroids) on the general infection rate and mortality in ventilated patients. RCT=randomized controlled trial; RR=relative risk (95% confidence intervals).

Manoeuvre	Author	Year	Study Design	n	Infection Rate	Mortality	GRADE
Immunonutrition	Beale	1999	Meta-analysis of 12 studies	1482	RR 0.67 (0.50-0.89) p=0.006	RR 0.05 (0.78-1.41) p=0.76	2A
	Heyland	2001	Meta-analysis of 22 studies	2419	RR 0.66 (0.54-0.80)	RR 1.1 (0.93-1.31)	2A
Steroids	Cronin	1995	Meta-analysis of 9 RCTs	1232	No difference	RR 1.13 (0.99-1.29)	2A
	Lefering	1995	Meta-analysis of 10 RCTs	1329	No difference	Difference in mortality -0.2% (-9.2 - 8.8)	2A
	Bollaert	1998	RCT	41	No difference	Difference in mortality 31% (1-61)	2A
	Briegel	1999	RCT	40	No difference	No difference	2A
	Annane	2002	RCT	300	No difference	Significant reduction	2A

Steroids

High doses of steroids given to septic patients are thought to be beneficial for three reasons. Steroids effectively suppress generalised inflammation due to micro-organisms and their toxins. Steroids have been shown to significantly reduce septic shock and early mortality within 72hrs. Steroids have been shown to significantly reduce mortality due to particular severe invasive infections including meningitis, typhoid and pneumocystes pneumonia (PCP). There have been a number of meta analyses and RCTs on the use of steroids in sepsis (Cronin L; Lefering R; Bollaert PE; Briegel J; Annane D 2002) (Table 2.6). The major perceived side effects of high-dose steroids are the associated immune suppression and subsequent risk of super-infections. Indeed the two meta-analyses show a trend towards increased mortality from secondary infection in patients receiving steroids. A recent systematic review by Annane in 2009 (Annane D 2009) examining the benefits and risks of steroids in sepsis reviewed 17 RCTs encompassing 2138 patients and 3 quasi-RCTs of 246 patients. Sub group analysis of prolonged low-dose corticosteroid therapy, suggests a beneficial drug effect on short-term mortality (Annane D 2009).

The COIITSS study (COIITSS Study) demonstrated that intensive insulin therapy together with hydrocortisone for septic shock did not improve in-hospital mortality. The addition of oral fludrocortisone did not result in a statistically significant improvement in in-hospital mortality (COIITSS Study).

It would appear that superinfections abolish the beneficial effects of steroids. A recent European study entitled 'Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1) influenza A infection' (Martin-Loeches I) was unable to demonstrates a benefit form using steroids in patients with H1N1 respiratory infections. However, it was unclear what the purpose of the corticosteroid therapy use was; whether it was for replacement therapy as advocated by (Annane D 2009) or for the control of inflammation (Sprung C).

Steroids are used in septic patients requiring treatment on the intensive care unit (ICU) for two reasons;

[i] at low doses (1mg/kg/day methylprednisone) for long periods as replacement therapy in patients with presumed relative adrenal insufficiency (Annane D 2009).

[ii] at high doses (5mg/kg/day) for four days in an attempt to block pro-inflammatory cytokine burst (Sprung C).

In the European H1N1 study low doses of methylprednisone (24mg/day) or prednisone (30mg/day) for two weeks were evaluated suggesting replacement therapy was used. Hence the results of this study seem to demonstrate that adrenal failure is not an important problem in H1N1 pneumonia as could be expected in a mono-organ disease. Consequently what this study does demonstrate and confirms is that prolonged steroid use is a risk factor for superinfections and that if patients with H1N1 pneumonia die, they die due to superinfections.

The major problem in H1N1 pneumonia is severely inflamed lungs. Modulation of this excessive inflammatory response provoked by the viral infection is an attractive pathophysiological concept. Short courses of high doses corticosteroids can down-regulate this inflammatory cytokine response.

The use of high dose steroids in severe sepsis and septic shock was abandoned in the 1980s as a result of the Sprung and Bone studies. However in the Sprung study a significant reduction of mortality was found during the first ten days in the treatment group (Sprung C). This early survival benefit disappeared due to the subsequent development of superinfections, generally occurring after one week. The Bone study (Bone RC), unfortunately providing only data on mortality at day 14, also demonstrated a high incidence of superinfection. Bone was the first to link superinfection with a high mortality.

Can the use of corticosteroids ever produce survival benefit if the importance of concurrent bacterial and/or fungal superinfections is not recognised? For example, in the Annane meta-analysis (Annane D, 2009) there were no superinfections and a

survival benefit was obtained. In contrast, in this European study superinfections were reported, and, hence no survival benefit.

Selective decontamination of the digestive tract has been acknowledged to be an effective and safe manoeuvre for the control of severe superinfections of lower airways and blood in the critically ill on the ICU (Liberati A 2009). SDD can prevent these lethal superinfections.

The question still remains, if in patients with severe inflammation such as H1N1 induced pneumonitis who remain clear of superinfection by applying SDD, is giving high dose steroids beneficial?

The next logical step would be to combine steroids with SDD whereby the perceived harmful effects of steroids could be abolished in that the early survival benefit from steroids can be preserved in keeping the patient free from secondary infections using SDD. The time has come to perform a randomized trial of SDD and steroids versus only SDD with the endpoint of mortality (Petros A).

Anti-inflammatory mediators

Almost 60 RCTs have been undertaken testing the hypothesis that modulation of the endogenous host inflammatory response can improve survival for patients with a clinical diagnosis of sepsis. The results have been frustrating and no new agent has been introduced into clinical practice (Marshall J).

Pooled data from studies using a monoclonal antibody to neutralise tumour necrosis factor demonstrate a statistically significant, 3.5% reduction in mortality. In aggregate, the three completed studies using recombinant intereleukin-1 (IL-1) receptor antagonists to neutralise IL-1 also showed an absolute mortality reduction of 5%. Natanson and colleagues (Zeni F) have shown that the combined results of all completed trials, independent of the therapeutic agents employed demonstrate a statistically significant 3% overall reduction in 28 day all cause mortality. It is debateable whether this small clinical benefit is sufficiently important to justify clinical use of these therapies, given the costs and potential toxicity of the agent involved.

Immunoglobulins

Polyclonal intravenous immunoglobulins significantly reduce mortality and can be used as an extra treatment option for sepsis and septic shock (Alejandria MM). Overall mortality was reduced in patients who received polyclonal intra-venous immunoglobulin (n=492; RR=0.64; 95% CI 0.51 to 0.80). For the two high-quality trials on polyclonal intra-venous immunoglobulin, the RR for overall mortality was 0.30, but the confidence interval was wide (95% CI 0.09 to 0.99, n=91). However, all the trials were small and the totality of the evidence is insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal intravenous immunoglobulins (IVIGs) remains experimental.

Activated protein-C

Drotrecogin alfa (activated), or recombinant human activated protein C, is thought to have anti-inflammatory, anti-thrombotic and profibrinolytic properties. In a randomized trial of 1690 patients the mortally rate was 30.8% in the placebo group and 24.7% in the drotrecogin alpha group, which translates into an absolute reduction in risk of death of 6.2% (p=0.05). The incidence of serious bleeding was higher in the drotrecogin alfa (activated) group that the placebo group (Bernard GR). This is level 1 evidence and grade B recommendation.

Tight Glucose Control

Van den Berghe et al demonstrated that intensive insulin therapy reduces morbidity and mortality in patients in cardiac surgical intensive care units (ICUs) (van den Berghe G 2001). However, intensive insulin therapy significantly reduced morbidity but not mortality among all patients in a medical ICU (Van den Berghe G 2006).

The American Diabetes Association and Surviving Sepsis Campaign recommend tight glucose control in critically ill patients based largely upon one trial that shows decreased mortality in a surgical intensive care unit. Because similar studies report conflicting results and tight glucose control can cause dangerous hypoglycemia, the data underlying this recommendation should be critically evaluated (Wiener RS).

In paediatric patients intensive insulin therapy to achieve age-adjusted normal fasting glucose concentrations improves short-term outcome of patients in PICU, in an RCT performed by Vlasselaers D et al in 2009. However, the NIRTURE study of tight glucose control in neonates and infants did not conclusively demonstrate the value of insulin therapy in preterm infants (Beardsall K).

The practice of tight glucose control is accompanied by an increased incidence of hypoglycaemia. Hermanides and colleagues (Hermanides J) demonstrated that hypoglycaemia increased the rate of death to 40/1000 in those who have experienced hypoglycaemia and 17/1000 who were not hypoglycaemic.

Antibiotic interventions

Selective Decontamination of the Digestive tract

SDD is based on the observation that critical illness changes body flora, promoting a shift from:

(i) Normal (*Streptococcus pneumoniae* in the throat and *Escherichia coli* in the gut) towards abnormal carriage (aerobic Gram-negative bacilli and methicillin-resistant Staphylococcus aureus in throat and gut) (Table 2.7).

(ii) Low to high grade carriage (gut overgrowth) of both normal and abnormal flora.

Parenteral cefotaxime controls gut overgrowth due to 'normal' bacteria, enteral polyenes control gut overgrowth due to 'normal' *Candida* species. Enteral polymyxin/tobramycin (without or with vancomycin) eradicate, if already present, and prevent overgrowth with 'abnormal' bacteria.

Gut overgrowth is the crucial event preceding endogenous infections (Table 2.8). Primary endogenous infection is caused by 'normal' and 'abnormal' potential pathogens, present in the patient's admission flora. This infection generally develops within a week and is the most frequent type of infection (55%). Secondary endogenous infection is invariably caused by 'abnormal' bacteria not present in the admission flora but acquired during treatment on the intensive care unit (ICU). This infection generally occurs after one week on ICU (30%). Exogenous infection is

caused by 'abnormal' bacteria never carried in the patient's oropharynx and/or gut. This type of infection may occur anytime during ICU-treatment (15%).

These three types of ICU-infection each require different prophylaxis. Primary endogenous can only be controlled by parenteral antimicrobials, secondary endogenous are prevented by enteral antimicrobials and high hygiene standards, exogenous are controlled by topical antimicrobials and hygiene.

These three interventions were first combined by Stoutenbeek who expanded the prophylaxis to include surveillance cultures creating the full four component SDD protocol, the main mechanism of action being gut overgrowth control (Figure 2.1) (Stoutenbeek CP 75 *ICM* 1984).

There are 64 randomized controlled trials evaluating SDD and 11 meta-analyses, confirming SDD reduces pneumonia (72%), septicaemia (37%) and mortality (29%) without resistance emerging (Table 2.9).

Bloodstream infection was the endpoint in 3 meta-analyses (Silvestri L 2005; Silvestri L 2007; Silvestri L AIC 2008), and was significantly reduced (OR 0.63, 95%CI 0.46-0.87). AGNB septicaemias were significantly reduced whereas Gram-positive ones were increased but not significantly due to the low incidence in the control group (Table 2.6). Multi-organ dysfunction syndrome was the endpoint in one of the most recent meta-analyses (Silvestri L 2010) and the relative reduction of 50% seen was significant. Mortality was the endpoint in 8 meta-analyses (Vandenbroucke-Grauls CMJ; D'Amico R; Safdar N; Liberati A 2004; Silvestri L *JCI* 2007; Silvestri L *JCC* 2009; Liberati A 2009; Silvestri L *CCM* 2010). SDD consistently reduced mortality as long as the sample size was large enough. The sample size was too small in 3 meta-analyses (Vandenbroucke-Grauls CMJ; Safdar N; Silvestri L *CCM* 2010).

Figure 2.1

The full four component protocol of SDD, that aims to control the three different types of infection that occur on ICU. PTA – poylmyxin/tobamycin/amphotericin.

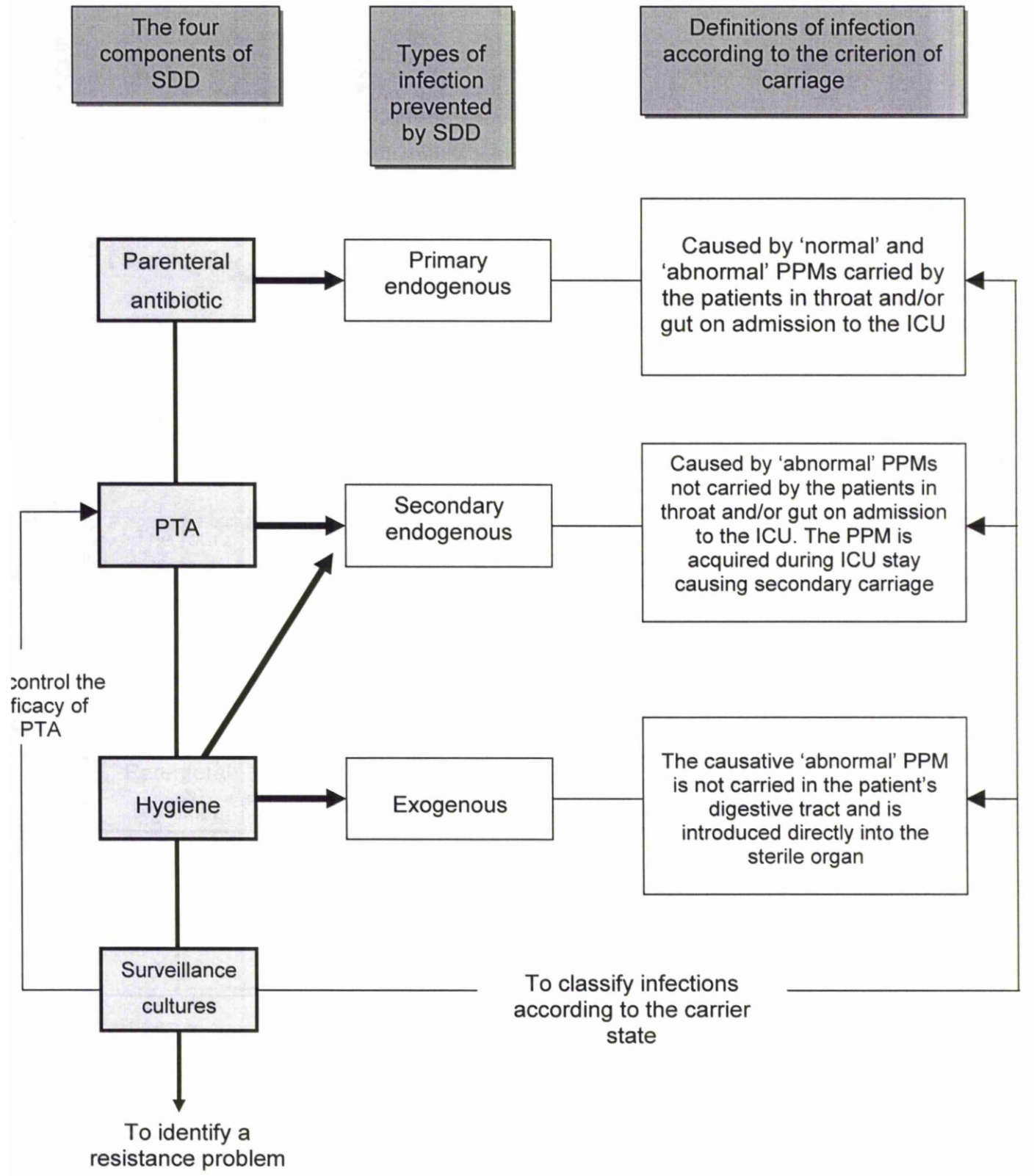


Table 2.7

Classification of micro-organisms based upon their intrinsic pathogenicity. The intrinsic pathogenicity index (IPI) is the ratio between the number of ICU patients with an infection due to a particular micro-organism and the number of ICU patients who carry the same particular micro-organism. Normal PPM are carried by healthy individuals in throat and gut. Individuals with an underlying condition carry both normal and abnormal PPM in throat and gut.

Intrinsic Pathogenicity		Site	Micro-organism	Flora
Low level IPI = 0.01	Indigenous flora	Throat	Peptostreptococci, Veillonella spp, Streptococcus viridans	Normal
		Gut	Bacteroides spp, Clostridium spp, enterococci, E. coli	
		Vagina	Peptostreptococci, Bacteroides spp, lactobacilli	
		Skin	Propionibacterium acnes, coagulase negative staphylococci	
Potential IPI = 0.3-0.6	Normal PPM	Throat	S. pneumoniae, H influenzae, Moraxella catarrhalis, S. aureus, Candida spp	Normal
		Gut	E. coli, S. aureus, Candida spp	
	Abnormal PPM	Throat & Gut	Klebsiella, Enterobacter, Citrobacter, Proteus, Morganella, Serratia, Pseudomonas, Acinetobacter spp, MRSA	Abnormal
High level IPI = 0.9-1.0	Epidemic Micro-organisms	Throat	Neisseria meningitidis	Abnormal
		Gut	Salmonella spp	

MRSA = methicillin-resistant Staphylococcus aureus

Morbidity vs. mortality as the important endpoint ?

SDD is an antimicrobial strategy aimed at preventing severe infections of lower airways and blood. It has been demonstrated to work successfully in adults but evidence for its success in children is less clear. Adults on ICU die of infections. The question is whether children die of infection. The clinical evidence supports the assumption that they do. Causes of infectious mortality include septicaemia, pneumonia, and meningitis. If there are a substantial proportion of children who die from infection then using SDD would make sense. The incidence of infection in a four-year prospective study in a large tertiary paediatric intensive care unit was 41.9% of all admissions (Sarginson R).

In adults, the pneumonia rate is 30% in children it is nearer 15% (Ruza F). In adults the septicaemia rate is 25% whereas in children it is 10% (Zobel G). So the morbidity due to infection is about third less in children compared to adults. The mortality is again about 30% in adults and in children it is about 5%. In the subgroup that requires ventilation for a minimum of four days it rises to 10% (Sarginson R).

So determining whether SDD can impact upon mortality in children is going to be difficult and is discussed further in Chapter 5.

Table 2.8

Carriage classification of severe infections of lower airways and blood.

Infection	PPM	Timing	Frequency	Manoeuvre
1. Primary endogenous	6 'normal' 9' abnormal'	<1 week	55%	Parenteral antimicrobials
2. Secondary endogenous	9 'abnormal'	>1 week	30%	Hygiene and enteral antimicrobials
3. Exogenous	9 'abnormal'	Anytime during ICU treatment	15%	Hygiene and topical antimicrobials

PPM = potentially pathogenic micro-organism;
6 'normal' PPM : *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Candida albicans, Staphylococcus aureus, Escherichia coli;*
9 'abnormal' PPM*: Klebsiella, Enterobacter, Citrobacter, Proteus, Morganella, Serratia, Acinetobacter, Pseudomonas* species and methicillin-resistant *Staphylococcus aureus* (MRSA)

Table 2.9 Overview of Efficacy of SDD: 64 RCTs and 11 meta-analyses.

Author	No RCTs	Sample Size	Lower airway infection OR (95%CI)	Bloodstream infection OR (95%CI)	Multiple Organ Dysfunction Syndrome OR (95%CI)	Mortality OR (95%CI)
Vandenbroucke-Grauls	6	491	0.12, 0.08 t o 0.19	NR		0.92, 0.45 to 1.84
D'Amico	33	5727	0.35, 0.29 to 0.41	NR		0.80, 0.69 to 0.93
Safdar	4	259	NR	NR		0.82, 0.22 to 2.45
Liberati	36	6922	0.35, 0.29 to 0.41	NR		0.78. 0.68 to 0.89
Silvestri yeasts	42	6075	NR	0.89, 0.16 to 4.95		NR
Silvestri	51	8065	NR	0.63, 0.46 to 0.87		0.74, 0.61 to 0.91
Silvestri G-ve G+ve	54	9473	 0.07, 0.04 to 0.13 0.52, 0.34 to 0.78	 0.36, 0.22 to 0.60 1.03, 0.75 to 1.41		 NR NR
Silvestri	21	4902	NR	NR		0.71, 0.61 to 0.82
Liberati	36	6914	0.28, 0.20 to 0.38	NR		0.75, 0.65 to 0.87
Silvestri	7	1270	NR	NR	0.50 0.34 to 0.74	0.82 0.51 to 1.32
Silvestri	12	2252	0.54, 0.42 to 0.69	NR		NR

Chapter 3

THE APPLICATION OF THE ADULT EVIDENCE FOR SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT TO THE PAEDIATRIC POPULATION

The purpose of this chapter is to evaluate the adult experience with selective digestive decontamination and its effect on mortality and severe respiratory and bloodstream infections in order to determine whether this may be extrapolated to the paediatric population. A literature search of the following databases was undertaken: Medline (1980-2010), Embase (1980-2010), CINAHL (1981-2010) and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (1989-2010). Keywords used were, paediatrics, children, infants, neonates, selective digestive decontamination, selective gut decontamination, selective oral decontamination, SDD, SGD, ventilator associated pneumonia, VAP prevention. Limits of English language were applied. Reference lists of retrieved articles were also reviewed. All articles in English identified from the literature search were evaluated.

All randomized controlled studies of SDD undertaken in adults or paediatrics were included in the review. 64 randomized controlled trials (RCTs) and 11 meta-analyses were identified of which 4 RCTs were conducted in paediatrics. Five of the 9 meta-analyses with the endpoint of mortality showed a significant survival benefit with the full SDD regimen. The six meta-analyses with the endpoint of lower airway infection showed a significant reduction. Three meta-analyses showed that the incidence of AGNB blood stream infections was significantly reduced. A meta-analysis of the 4 paediatric trials showed an effect on paediatric morbidity but not mortality. SDD reduces mortality and severe respiratory and systemic infections in adults. There is limited evidence for the use of SDD in paediatrics. Paediatric patients have been shown to follow the same pattern of primary endogenous, secondary endogenous and exogenous infection as adults; the adult information is likely to be generalisable

to the paediatric population. To achieve a significant survival benefit in paediatrics a much larger number of children would need to be studied.

Background

Selective Digestive Decontamination has been advocated as a prophylactic antimicrobial manoever for patients requiring intensive care (Almuslim O). Since its introduction 25 years ago Level 1 evidence has accrued to unequivocally support the effectiveness of SDD at reducing severe lower airway and blood stream infections in patients in adult intensive care units (van Saene HK *JCC* 2009).

The oropharyngeal cavity and gastrointestinal tract play an important role in the pathogenesis of pneumonia and septicemia in critically ill patients. Migration and translocation of aerobic gram-negative bacilli (AGNB) and methicillin-resistant staphylococcus aureus (MRSA) may occur and result in respiratory tract and blood stream infections (Baxby D). Primary carriage is where the patient is admitted with flora in the digestive tract, and secondary carriage occurs when the patient acquires flora in the digestive tract whilst having treatment on the intensive care unit. SDD aims to prevent secondary carriage of hospital acquired or "abnormal" flora, including AGNB and MRSA and yeasts by the enteral application of antibiotics and antifungals to the oropharynx and gastro-intestinal system. Many advocates of SDD also recommend the use of a parenteral cephalosporin, usually cefotaxime, as an essential component of the SDD regimen for the first three to four days, in order to treat any primary endogenous infection and to clear carriage of community acquired or "normal" flora such as *S.aureus* and *E.coli* (Stoutenbeek CP *JoT* 1987).

Gut overgrowth (van Saene HKF *JHI* 1996) may harm the critically ill in four main ways:

(i) Inflammation – overgrowth of abnormal AGNB and production of endotoxin has been shown to lead to cytokinaemia and inflammation of major organ systems (Baue AE).

(ii) Immunosuppression – overgrowth of abnormal AGNB (and associated endotoxin production) has been shown to impair immunity due to generalised inflammation following absorption of AGNB and/or endotoxin (Deitch EA).

(iii) Infection – there is a quantitative relationship between surveillance and diagnostic samples. When there is overgrowth in surveillance samples the diagnostic samples become positive which is the first stage in the development of infection (Van Uffelen R).

(iv) Resistance – the abnormal carrier state in overgrowth concentrations guarantees increased spontaneous mutation leading to polyclonality and antibiotic resistance (van Saene HKF *CDT* 2008).

SDD is a prophylactic measure using selected antimicrobials to control overgrowth of both "normal" and "abnormal" flora, thereby reducing the four harmful side-effects of overgrowth i.e. control of inflammation (Conraads VM) restoration of suppressed systemic immunity (Horton JW); infection prevention (de la Cal MA *JHI* 1994) and resistance control (van Saene HKF D 2004).

There have been three recent reports describing the efficacy of SDD in children (Sarginson RE *CCM* 2004; (Paulus S *EJC* 2005); Thorburn K *CMI* 2006. However, these are observational single-centre studies. Therefore the aim was to assess the efficacy and adverse effects of SDD in the paediatric population from the available evidence, and contrast this with adult evidence.

What is selective decontamination of the digestive tract?

SDD is an antimicrobial strategy aimed at preventing infection using prophylactic parenteral and enteral antimicrobials. It is based upon two fundamental principles; pathogenesis of infection is due to a limited range of potential pathogens, and the three types of pathogenic pathway each require a different intervention.

SDD defines 15 potential pathogens (van Saene HKF *ICM* 2003). There are six "normal" potential pathogens (*Streptococcus pneumoniae, Haemophilus influenzae,*

Moraxella catarrhalis, Staphylococcus aureus, Escherichia coli and Candida albicans) as well as nine "abnormal" pathogens (van Saene HKF *ICM* 2003). The abnormal pathogens consist of eight AGNBs (*Klebsiella, Citrobacter, Enterobacter, Proteus, Morganella, Serratia, Acinetobacter and Pseudomonas* species) and MRSA (van Saene HKF *ICM* 2003).

The three pathogenic pathways for infection defined by the criterion of carriage are primary endogenous, secondary endogenous and exogenous infection. Primary endogenous infection generally develops within a week and is the most frequent type of infection, responsible for approximately 55% of infections (Sarginson RE *CCM* 2004; Silvestri L *JHI* 1999; de la Cal MA *Chest* 2001). This type of infection is caused by potential pathogens which are present in the admission (oropharynx or gut) flora and may be either normal or abnormal flora. Secondary endogenous infection is generally caused by abnormal bacteria not present in the admission flora but acquired during treatment on the ICU. This type of infection generally occurs after one week and represents approximately 30% of infections (Sarginson RE *CCM* 2004; Silvestri L *JHI* 1999; de la Cal MA *Chest* 2001). Finally, exogenous infection is caused by abnormal potential pathogens never carried in the digestive tract but introduced directly into the patient from an external source. Exogenous infection may occur at any time during ICU treatment, and accounts for approximately 15% of infections (Silvestri L *JHI* 2005).

Table 3.1 and 3.2 describe the full four component SDD regimen and the rationale for its use. Elimination of the primary endogenous route requires an initial course of parenteral antimicrobials in order to eradicate carriage of normal flora and to treat any pre-existing infection (Baxby D; Stoutenbeek CP *ICM* 1984). Cefotaxime was originally chosen because of its broad spectrum of activity against normal flora and the majority of the AGNB (Baxby D) and because of it's high salivary and biliary concentrations render it a highly effective antimicrobial for eradication of oropharyngeal and gut carriage of normal flora (Stoutenbeek CP *JoT* 1987).

To prevent secondary endogenous infection, the antimicrobials polymyxin, tobramycin and amphotericin B are administered enterally to prevent the acquisition of abnormal flora and to eradicate any abnormal flora the patient may already be

carrying. If there is a delay in administering the enteral antibiotics, secondary endogenous infection may occur, this should be treated via the parenteral route. The combination of enteral polymyxin and tobramycin (Kucers') was chosen because it covers all abnormal AGNB including *Pseudomonas* species, in addition to being synergistic (Kuipers JS). There are five different polymyxin preparations, A-E, however only two are clinically available, B and E (colistin). Colistin is the only enteral polymyxin available in the United Kingdom (Martin J). Enteral polyenes such as amphotericin B and nystatin are used to clear 'normal' fungal carriage, (Hofstra W 1979; Hofstra W 1982). Enteral vancomycin is only added to the polymyxin /tobramycin/amphotericin B combination in cases of MRSA endemicity in order to eradicate and clear the MRSA carrier state (Silvestri L *AJIC* 2002).

Standard hygiene measures and scrupulous attention to sterile technique is crucial in order to prevent the introduction of potential pathogens from external sources directly into sterile organs, bypassing the carrier state. Again, polymyxin E (or colistin), tobramycin, amphotericin B and vancomycin (if MRSA is endemic) are used topically, e.g. in a paste on a tracheostomy site, to prevent exogenous lower airway infections (Veelo DP).

The fourth component of the SDD regimen is the use of surveillance cultures in order to monitor the efficacy of the SDD protocol and the development of antimicrobial resistance. These three interventions were first combined by Stoutenbeek in 1984 (Stoutenbeek CP *ICM* 1984), who then went on to further develop the SDD regimen by adding this final component of surveillance cultures.

Efficacy

There are 64 randomized controlled trials (RCTs) (Abdel-Razek SM; Abele-Horn M; Aerdts SJ; Arnow PM; Barret J; Bergmans DC; Bion JF; Blair P; Boland JP; Bouter H; Brun-Buisson C; Camus C; Cerra FB; Cockerill FR 3rd; de Jonge E; de La Cal MA AS 2005; de Smet AM; Diepenhorst GM; Farran L ; Ferrer M; Finch RG; Flaherty J; Gastinne H; Gaussorgues PH ; Georges B ; Gosney M; Hammond JM; Hellinger WC; Jacobs S; Kerver AJ; Korinek AM; Krueger WA; Laggner AN; Lingnau W; Luiten EJ; Martinez-Pellús AE *CCM* 1993; Martinez-Pellús *AEICM* 1997; Oudhuis GJ;

Table 3.1 - The full four components of SDD, described in detail. Doses are given, organisms targeted and route advocated.

SDD Component	Targeted Potential Pathogens	Antimicrobial Agent	Adult Dose	Route
1. Parenteral antibiotics (Baxby D, Stoutenbeek CP *ICM* 1984)	Primary endogenous infections: 'normal' and 'abnormal' flora	cefotaxime	1g four times daily (de Jonge E, Stoutenbeek CP ICM 2007)	Intravenously for the first 4 days (de Jonge E, Stoutenbeek CP *ICM* 2007)
2. Enteral application of antibiotics and antifungals (Baxby D, Stoutenbeek CP *ICM* 1984)	Secondary endogenous infections of oropharynx: - AGNB - Yeasts - MRSA	polymyxin E with tobramycin amphotericin B vancomycin*	2g of 2% paste or gel four times daily (Baxby D, Stoutenbeek CP, *ICM* 1984) 2g of 2% paste or gel four times daily (Baxby D, Stoutenbeek CP, *ICM* 1984) 2g of 4% paste or gel four times daily (Silvestri L, *ERJ* 2004)	Enterally to oropharynx/ buccal mucosa (Baxby D, Stoutenbeek CP, *ICM* 1984, Silvestri L, *ERJ* 2004.)
	Secondary endogenous infections of gut: - AGNB - Yeasts - MRSA	polymyxin E with tobramycin amphotericin B or nystatin vancomycin*	100mg four times daily (Baxby D, Stoutenbeek CP, *ICM* 1984 80mg four times daily (Baxby D, Stoutenbeek CP, *ICM* 1984) 500mg four times daily (Baxby D, Stoutenbeek CP, *ICM* 1984) 2 x 10^6 units four times daily (Cockerill FR 3rd, Wiener J) 500mg four times daily (Silvestri L AJC 2002)	Enterally or via nasogastric tube Baxby D, Stoutenbeek CP, *ICM* 1984, Silvestri L *AJIC* 2002,Cockerill FR 3rd, Wiener J
3. Appropriate infection control practices on the ICU (Baxby D, Stoutenbeek CP, ICM 1984) and topical antimicrobials (Veelo DP)	Exogenous infections: - AGNB - Yeasts - MRSA	polymyxin E with tobramycin amphotericin B vancomycin*	2g of 2% paste or gel four times daily (Veelo DP) 2g of 2% paste or gel four times daily (Veelo DP) 2g of 4% paste or gel four times daily (Silvestri L ERJ 2004)	Topically to external sites eg tracheostomy (Veelo DP)
4. Throat and rectal surveillance cultures (Baxby D)	To monitor efficacy and development of resistance – on admission and twice weekly (Baxby D)			

Abbreviations: AGNB: Aerobic Gram Negative Bacteria; MRSA: methicillin resistant Staphylococcus aureus

* Vancomycin is only required if MRSA is endemic (Silverstri L 2002)

Table 3.2 - Rationale for the four components of SDD (Baxby D; Stoutenbeek CP *ICM* 1984).

Component	Rationale
Parenteral antibiotics for first 3-4 days of therapy	To control primary endogenous infections
Hygiene and enteral application of antibiotics and antifungals into the throat and gut for the duration of intubation/ICU stay	To control secondary carriage and development of subsequent secondary endogenous infections
Appropriate infection control practices on the ICU, optimal level of hygiene and topical antibiotics	To control exogenous infections
Throat and rectal cultures on initiation of therapy and twice weekly	To monitor efficacy and development of resistance

Palomar M; Pneumatikos I; Pugin J; Quinio B; Rayes N; Rios F; Rocha LA; Rodríguez-Roldán JM; Rolando N *Hep* 1993; Rolando N *LTS* 1996; Ruza F; Snachez Garcia M; Schardey HM; Smith SD; Stoutenbeek CP 1996; Stoutenbeek CP *ICM* 2007; Tetteroo GW; Ulrich C; Unertl K; Verwaest C; Wiener J; Winter R; Yilmazlar A; Yu J; Zobel G; Zwaveling JH) and eleven meta-analyses of only RCTs (Vandenbroucke-Grauls CMJ; D'Amico R; Safdar N; Liberati A; Silvestri L *ICM* 2005; Silvestri L *JHI* 2007; Silvestri L *AIC* 2008; Silvestri L *JCC* 2009; Liberati A *Cochrane* 2009; Silvestri L *CCM* 2010) that assess the efficacy of SDD in reducing mortality and respiratory and bloodstream infections (Tables 3.3, 3.4). All but four of these RCTs were conducted in adults.

Six meta-analyses have the endpoint of lower airway infection (Vandenbroucke-Grauls CMJ; D'Amico R; Liberati A 2004; Silvestri L *AIC* 2008; Liberati A). All invariably show a significant reduction of lower airway infections due to both Gram-negative and Gram-positive bacteria.

There are nine meta-analyses with the endpoint of mortality (Vandenbroucke-Grauls CMJ; D'Amico R; Safdar N; Liberati A 2004; Silvestri L *JHI* 2007; Silvestri L *JCC* 2009; Liberati A 2009; Silvestri L *CCM* 2010; Petros A). Five of the nine, with sample sizes between 4,902 and 8,065 patients, consistently show a significant survival benefit with the full SDD regimen (D'Amico R MJ 1998; Liberati A 2004; Silvestri L *JHI* 2007; Silvestri L *JCC* 2009; Liberati A 2009). In the other four meta-analyses the mortality reduction was not significant, due to the small sample size (259, 335, 491 and 1270 patients) (Vandenbroucke-Grauls CMJ; Safdar N; Silvestri L *CCM* 2010; Petros A).

The significant survival benefit seen is in all likelihood due to the control of severe infections of not just lower airways but also the bloodstream. Three of the meta-analyses have the endpoint of septicemia/bloodstream infections, (Silvestri ICM 2005; Silvestri L *JHI* 2007; Silvestri L *AIC* 2008). If classified by causal microorganism, the incidence of AGNB, a major cause of mortality, was significantly reduced, (Silvestri L *HI* 2007; Silvestri L *AIC* 2008). However, bloodstream infections caused by Gram-positive organisms did not increase but not significantly (Silvestri L *JHI* 2007; Silvestri L *AIC* 2008), refuting concerns that SDD promotes Gram-positive

infections (Kallet R). Blood stream infections due to fungi were non-significantly reduced (OR 0.89, 95%CI 0.16-4.95) due to the low event rate in the control group (Silvestri L *ICM* 2005). Finally, one of the most recent meta-analyses demonstrates that SDD using the full SDD regimen of both parenteral and enteral antimicrobials reduces multiple organ failure dysfunction syndrome (MODS) by 50% (Silvestri L *CCM* 2010).

SDD in Paediatrics

Paediatric patients follow the adult model of primary endogenous, secondary endogenous and exogenous infections (Stoutenbeek CP *JoT* 1987) therefore the results of the adult studies and meta-analyses are likely to be generalisable to the paediatric population.

The mortality rate in children is between 5-10% depending on their severity of illness, as assessed by the PIM score and type of injury or underlying illness. The mortality rate in UK PICUs between 1998 and 2006 was 4.9% (Smit M). So any manoeuvre, which attempts to prove a reduction in mortality, will have to have a very large sample size to prove statistical significance. For example, to demonstrate a significant reduction in any adult study which has a 30% incidence of an event, then 5000 patients need to be included in the study. For children, using a mortality rate of 5%, approximately 10,000 children would need to be enrolled in any RCT to demonstrate a significant difference clearly not a realistic option. It is thus easier to demonstrate a reduction in morbidity rather than mortality in children.

Four RCTs of SDD have been performed in children between 1991 and 2001 and include a total of 335 patients (Barret JP; Ruza F; Smith SD; Zobel G) (Table 3.5). Zobel G et al were the first to undertake a prospective randomized controlled trial of SDD in paediatrics in 1991. The primary endpoint of their study was the effect on colonisation and infection rates of AGNB and yeasts in the oropharynx, gut and respiratory tracts of critically ill children on the paediatric intensive care unit. 25 children were randomized to receive the full 4-component SDD regimen, and 25 were randomized to the control group and received either perioperative antibiotic prophylaxis or antibiotic therapy if indicated by clinical or microbiological evidence of

infection. Both groups were comparable in terms of baseline age, weight, sex and severity of illness. The investigators found that colonisation with Gram-negative micro-organisms and yeasts in the oropharynx and digestive and respiratory tracts increased rapidly in up to 52% of patients in the control group versus no colonisation in the treatment group ($p<0.01$), and the rate of acquired secondary infections was 36% in the control group and 8% in the treatment group ($p<0.025$). There was no significant difference between the groups in the duration of intensive care, mechanical ventilation or mortality rate. This study used gentamicin as the enteral aminoglycoside component and found detectable serum gentamicin levels of 1.5 ± 0.18mg/L. No adverse effects were attributed to SDD.

In 1993 Smith et al undertook a prospective RCT of SDD in 36 paediatric orthotopic liver transplant patients, in order to determine whether SDD influenced the rate of post-operative infections (Smith SD). Patient groups were well matched in terms of baseline characteristics. While the difference in effect between the treatment and control groups may have been attenuated as both groups received intravenous cefotaxime, and SDD treatment was only continued until feeding resumed, this study still found significantly fewer patients with acquired secondary Gram-negative infections in the treatment group (8% vs 36%, $p<0.001$), as well as a significant reduction in AGNB in the stool ($p<0.05$) which returned to baseline by 3 weeks. Gram-positive and anaerobic organisms were unaffected and there was no significant difference in the incidence of fungal infections. ICU length of stay, total hospital length of stay and mortality were not significantly different between the two groups. Mild diarrhoea occurred in 6 of the 18 patients in the treatment group, but did not require early discontinuation of SDD and resolved when SDD treatment was terminated.

Ruza et al undertook a prospective RCT of the enteral components in 244 PICU patients aged 1 month to 14 years old with neurological coma, in order to determine the incidence of nosocomial infection. 100 patients were randomized to receive SDD treatment, 116 patients to control, 18 patients were withdrawn due to protocol violation. Both groups were well matched in terms of age, sex, diagnosis on admission, and multi-organ system failure (MOSF) scores. However, therapeutic intervention scoring system (TISS) scores, number of organ systems affected, and

number of patients who were mechanically ventilated were significantly higher at baseline in the SDD group. No significant reduction in antibiotic use, length of stay or mortality was seen with SDD, which was in all likelihood due to the small sample size. Univariant analysis found no significant reduction in incidence of nosocomial infections with SDD, but multivariant analysis found that SDD acted as a protective factor for >90% of the sample with respect to respiratory and urinary tract infections, reducing the risk to 1 in 5 (odds ratio: 0.21) and 1 in 3 (odds ratio: 0.33), respectively. Analysis using the intention to treat model, incorporating the withdrawn patients, would have strengthened the reliability of the conclusions. The full four-component regimen has been seen to provide the greatest efficacy in adults, as discussed above, therefore results may have been improved had oropharyngeal component and the intravenous component also been utilised in the treatment group. No adverse effects were attributed to SDD in the 116 patients in the treatment group.

The last paediatric RCT reported in the literature was conducted in 2001 by Barret et al. (Barret JP) who investigated the use of the enteral SDD components in paediatric patients with severe burns, in order to determine bacterial colonisation of the digestive tract and burn wounds and the incidence of nosocomial infections and septic complications. 11 patients were randomized to the treatment group and 12 randomized to placebo. No significant differences were seen in the colonisation rates of burn wounds, sputum, nasogastric aspirates or faeces. Similar incidences of pneumonia, sepsis and other complications had similar incidences in both groups, but patients in the SDD group had a significantly higher incidence of diarrhoea ($p=0.003$). This study only utilised the enteral component of SDD; combined with the very small subject numbers this may have accounted for the non-significant results, as the oropharyngeal component is essential for the control of respiratory tract infections (Stoutenbeek CP *JoT* 1987).

The results from the four paediatric RCTs have been analysed in a meta-analysis (Petros A). Overall mortality for SDD vs. control children was 13 of 170 (6.7%) and 11 of 163 (7.6%), respectively, demonstrating a non-significant reduction in the odds of death (odds ratio, 1.18; 95% confidence interval, 0.50-2.76; $p = 0.70$). In three studies including 109 children, infection was demonstrated in 10 of 54 (13%) patients

in the SDD group and 24 of 55 (15.9%) in the controls (odds ratio, 0.34; 95% confidence interval, 0.05-2.18; p = 0.25). Pneumonia was diagnosed in 5 of 170 patients (2.9%) in the SDD group and in 16 of 163 patients (9.8%) in the control group (odds ratio, 0.31; 95%CI, 0.11-0.87; p=0.027). Therefore even with these small patient numbers, there was a significant reduction in infectious morbidity in the paediatric population.

No further RCTs of SDD in paediatrics have been reported in the literature in the last decade. Paulus et al. undertook an observational study of SDD in the setting of a children's haematology/oncology unit, and concluded that addition of SDD to systemic antibiotics maintained a low level of resistance and mortality (Paulus, S). The lack of any randomisation or control group in this study renders it as high risk for internal selection and investigator bias, and further verification of these results in the form of a randomized controlled trial is necessary. However, this study is useful due to the encouraging lack of microbiological resistance seen with SDD over the three year duration of the study and the extremely low incidence of secondary endogenous infection seen with SDD. No specific adverse effects were attributed to the use of SDD in this paediatric study.

Table 3.6 describes a paediatric dosage regimen (Kucers JS) for SDD and Table 3.7 the UK licensing status, presentation & cost for the individual components.

Adverse Effects

Absorption of the enteral products from the gastrointestinal tract appears negligible; therefore systemic adverse effects are likely to be minimal unless the integrity of the gut wall is breached. Adverse effects include the risk of antibiotic resistance (Almuslim O), possibility of blockage of nasogastric tubes by the enteral medication (Smit M) and diarrhoea in paediatric patients (Barret JP; Smith SD). Diarrhoea has not been associated with SDD in adult critically ill patients (van der Spoel JI). The diarrhoea in paediatric patients may be due to the high osmolality of the suspension pulling in fluid into the gut. Total obstruction of the oesophagus and jejunum due to accumulation of oral paste has been described in three adult patients (Smit M,) but not in paediatrics to date.

Antimicrobial resistance

There is an anecdotal report of one centre involved in the de Smet et al. national RCT of SDD (de Smet AM) that has since experienced the first serious vancomycin resistant enterococcus (VRE) epidemic in their hospital, resulting in temporary closure of four ICUs (Meessen N). At Alder Hey the isolation of four plasmid-mediated extended-spectrum β-lactamase positive multi-drug resistant (MDR) strains was reported from four patients receiving SDD who were not previously carriers of these MDR strains prior to their admission to the ICU, which was felt to be associated with use of the intravenous cefotaxime component of SDD (Abecasis F).

Adverse effects of the individual components of SDD

Colistin (colistimethate sodium, polymyxin E) oral liquid: No specific adverse effects have been documented with enteral colistin. Colistin is not absorbed via the enteral route in paediatrics (Martin J). However, it may be absorbed from the gastro-intestinal tract in infants less than six months old (Kucers'; Martin J). Adverse effects, particularly neurotoxicity are more likely with excessive intravenous doses. These effects would be unlikely with enteral administration.

Tobramycin base oral liquid: Aminoglycosides are not absorbed from the gut, although there is a risk of absorption in patients with inflammatory bowel disease and liver impairment (Martin J). High (toxic) serum levels of tobramycin have been observed in adult patients receiving SDD who have severe renal impairment requiring continuous veno-venous haemofiltration (CVVH) (Mol M). Detectable serum levels of tobramycin have also been seen in a patient with normal renal function with bowel perforation receiving SDD (Posthouwer D). Intravenous tobramycin, like any aminoglycoside may cause ototoxicity and nephrotoxicity, and may impair neuromuscular transmission, therefore are contraindicated in children with myasthenia gravis (Martin J). While no specific adverse effects have been attributed to enteral tobramycin in paediatric patients receiving SDD, it would seem prudent, in light of enteral absorption seen with gentamicin use in earlier SDD paediatric trials (Zobel G) that serum tobramycin levels are monitored particularly if renal or liver function is impaired, the patient is on any form of renal replacement

therapy or if there is any suspicion that the patient may be at risk of increased absorption due to gastrointestinal disease. SDD should be avoided in paediatric patients with myasthenia gravis.

Amphotericin B oral liquid: Enteral absorption is minimal. Adverse effects include rash, glossitis, nausea, vomiting, diarrhoea, irritation of skin and mucous membranes and rarely hypersensitivity (Dermapharm AG). Amphotericin B liquid also contains parabens, sodium benzoate and sodium metabisulphite, which may cause allergic reactions including anaphylaxis and bronchospasm particularly in patients with a history of asthma (Dermapharm AG).

Summary

SDD is a well studied prophylactic regimen for preventing nosocomial infections in intensive care patients. Evidence from randomized controlled trials and meta-analyses in critically ill adult patients demonstrates a significant benefit in terms of reduction in respiratory tract and blood stream infections and mortality with the use of SDD as antibiotic prophylaxis in the setting of intensive care units with a low level of endemic antibiotic resistance. SDD is a safe intervention with minimal adverse effects. The assertion that development of antimicrobial resistance is a risk with SDD is not supported by the current available literature and is thus far limited to anecdotal reports and opinion.

Information from studies in adults may be applicable to the paediatric ICU population, which has been shown to follow the same pattern of primary endogenous, secondary endogenous and exogenous infection. To achieve a significant survival benefit in paediatrics a much larger number of children would have to be studied. Despite the small number of paediatric patients in a limited number of RCTs there is still a demonstrable reduction in morbidity in children.

Table 3.3 - Details of the eleven meta-analyses of RCTs assessing the effectiveness of SDD in reducing morbidity (lower airway and bloodstream infections and multiple organ failure) and mortality.

Author	Year	Population	Numbers Enrolled		Study type included in meta-analysis	Lower Airway / Overall Infections	Blood Stream Infections	Multiple Organ Dysfunction Syndrome	Overall Mortality	Comments
			Trials	Patients		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	
Vandenbroucke-Grauls CMJ	1991	Intensive Care. RTI	6 6	998 491	HCs RCTs + AA	0.21 (0.15-0.29) 0.12 (0.08-0.19)	NA	NA	0.91 (0.67-1.23) 0.70 (0.45-1.09)	Historical controls RCTs + alternate allocation trial
D'Amico R	1998	Intensive Care. RTI	16 17	3361 2366	RCTs RCTs	0.35 (0.29-0.41) 0.56 (0.46-0.68)	NA	NA	0.80 (0.69-0.93) 1.01 (0.84-1.22)	Enteral plus systemic Only enteral antibiotics
Safdar N	2004	Liver transplant	4	259	RCTs	RR 0.88 (0.71-1.1) RR 0.16 (0.07-0.37)	NA	NA	RR 0.82 (0.22-2.45)	Overall infections AGNB infections
Liberati A	2004	Intensive Care. RTI	36	6922	RCTs	0.35 (0.29-0.41) 0.52 (0.43-0.63)	NA	NA	0.78 (0.68-0.89) 0.97 (0.81-1.16)	Enteral plus systemic Only enteral antibiotics
Silvestri L	2005	Fungal infections	42	6075	RCTs	0.32 (0.19-0.53) 0.30 (0.17-0.53)	0.89 (0.16-4.95)	NA	NA	Fungal carriage Overall fungal infections
Silvestri L	2007	Intensive Care. BSI	31 16 16 16	4527 2097 2097 3331	RCTs RCTs RCTs RCTs	NA	0.73 (0.59-0.90) 0.39 (0.24-0.63) 1.06 (0.77-1.47) 0.63 (0.46-0.97)	NA	0.80 (0.69-0.94) 0.74 (0.61-0.91)	Overall blood infections G-ve blood infections G+ve blood infections Sub-group analysis of full regimen (IV + enteral)

Silvestri L et al	2008	Intensive Care. Carriage	54	9473	RCTs RCTs RCTs	0.11 (0.06-0.20) 0.52 (0.34-0.78) 0.07 (0.04-0.13)	0.35 (0.21-0.67) 1.03 (0.75-1.41) 0.36 (0.22-0.60)	NA	NA	G-ve infections G+ve infections Sub-group analysis of full regimen (IV + enteral)
Silvestri L et al	2009	All RCTs	21	4902	RCTs	NA	NA	NA	0.71 (0.61-0.82)	
Liberati A et al	2009	Intensive Care RTI	36	6914	RCTs	0.28 (0.20-0.38)	NA	NA	0.75 (0.65-0.87)	
Silvestri L et al	2010	Intensive Care	7	1270	RCTs	NA	NA	0.50 (0.34-0.74)	0.82 (0.51-1.32)	
Petros A et al	2011	Pediatrics	4	335	RCTs RCTs	0.31 (0.11-0.87) 0.34 (0.05-2.18)	NA	NA	1.18 (0.50-2.76)	Pneumonia Overall Infection

Abbreviations: AA: Alternate Allocation; AGNB: Aerobic Gram Negative Bacteria; BMT: Bone Marrow Transplant; BSI: Blood Stream Infection; CI: Confidence Interval; HC: Historical Controls; IV: Intravenous; NA: Not Assessed; OR: Odds Ratio; RCTs: Randomised Controlled Trials; RTI: Respiratory Tract Infection; SDD: Selective Decontamination of the Digestive Tract.

Table 3.4

Detailed description of the eleven meta-analyses of RCTs assessing the effectiveness of SDD in reducing morbidity (lower airway and bloodstream infections and multiple organ failure) and mortality.

Study 1: 1991 Vandenbroucke-Grauls CMJ	Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit.
Inclusion criteria	All comparative studies on SDD done in ICUs and published from Jan 1984-Dec 1990; included those with historical controls, one in which patients were alternately allocated to study or control group, and RCTs. Exclusion criteria: Not specified 11 trials included; 1489 patients.
Measurements	Outcome measures: To assess the effect of SDD on respiratory tract infections and survival.
Results	Historical control studies: SDD significantly reduced respiratory tract infections (OR 0.21; 95% CI: 0.15-0.29). RCTs + alternate allocation trial: SDD significantly reduced respiratory tract infections (OR 0.12; 95% CI 0.08-0.19). Studies with historical controls and RCTs showed no significant mortality difference between SDD and control (OR 0.91; 95% CI 0.67-1.23 for historical controls; OR 0.70; 95% CI 0.45-1.09 for RCTs + alternate allocation trial).
Comments	No methodological selection criteria used. Did not include unpublished studies. Sample size may have been too small to demonstrate a reduction in mortality.

Study 2: 1998 D'Amico R	Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomized controlled trials.
Inclusion criteria	All published and unpublished RCTs from 1984 to 1996 which examined the effect of antibiotic prophylaxis for the prevention of respiratory tract infections and death in unselected critically ill adult patients. No language restriction. Exclusion criteria: Studies without proper randomisation, those based on pre-selected patient populations, or where patients did not undergo >48 hours of mechanical ventilation. 33 RCTs included; 5727 critically ill adult patients.
Measurements	Outcome measures: To assess the effect of different forms of antibiotic prophylaxis on respiratory tract infections and total mortality.
Results	Estimates from aggregate data meta-analysis of 16 trials (3361 patients) that tested combined treatment (enteral plus systemic antibiotics) indicated a significant reduction in infection (OR 0.35; 95% CI 0.29-0.41) and total mortality (OR 0.80; 95% CI 0.69-0.93). Analysis of 17 trials (2366 patients) that tested only enteral antibiotics found a significant reduction in infection (OR 0.56; 95% CI 0.46-0.68) without a significant effect on total mortality (OR 1.01; 95% CI 0.84-1.22).
Comments	Unpublished studies included, decreasing risk of publication bias.

Study 3: 2004 Safdar N	The role of selective decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis.
Inclusion criteria	All published English-language studies that evaluated the efficacy of SDD in liver transplant patients. RCTs that included liver transplant patients given SDD vs placebo, no treatment, or minimal treatment (oral nystatin alone) that provided enough data to calculate a relative risk ratio were included in the meta-analysis. Exclusion criteria: Non-English-language studies. 15 studies included in systematic review, of which 5 were RCTs, 4 of which were include in the meta-analysis (259 patients) (1 RCT excluded from meta-analysis because data on overall infections in the two groups was not provided.
Measurements	Objectives: To determine whether SDD is beneficial in reducing infections overall, and those caused by Gram-negative bacteria in patients following liver transplantation.
Results	The effect on overall infection was limited in the 4 RCTs, pooled RR 0.88 (95% CI 0.7-1.1) indicating no statistically significant reduction in infection with the use of SDD. The summary risk ratio for the association between SDD and Gram-negative infection was 0.16 (95% CI 0.07-0.37), indicating an 84% relative risk reduction in the incidence of Gram-negative infections in patients receiving SDD. The summary risk ratio for the association between SDD and mortality was 0.82 (95% CI 0.22-2.45) indicating no significant benefit in reducing mortality.
Comments	Included selected patient populations (post liver transplant patients). Did not include non-English-language studies, risking publication bias. Two authors independently assessed studies for inclusion. SDD regimens and duration varied widely amongst studies. Sample size may have been too small to demonstrate a reduction in mortality

Study 4: 2004 Liberati A	Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care.
Inclusion criteria	All unselected RCTs, published and unpublished, testing the effect of antibiotics prophylaxis for the prevention of respiratory tract infection or death. Exclusion criteria: Studies based on pre-selected patient groups and studies where >50% of patients did not undergo mechanical ventilation. 36 RCTs included; 6922 patients.
Measurements	Outcome measures: To assess the effects of SDD on preventing respiratory tract infections and overall mortality in adults receiving intensive care. To determine whether enteral antibiotics alone or combination of enteral and systemic antibiotics are effective at reducing mortality.
Results	Patients treated with SDD consisting of a enteral and systemic antibiotic component had a significant reduction in respiratory tract infections (OR 0.35; 95% CI 0.29-0.41) and mortality (odds ratio 0.78; 95% CI 0.68-0.89). On average 5 patients needed to be treated to prevent one respiratory tract infection and 21 to prevent one death. Patients treated with enteral antimicrobials alone had significant reduction in respiratory tract infections (OR 0.52, 95% CI 0.43-0.63) but not in total mortality (OR 0.97, 95%CI 0.81-1.16). No effect on antibiotic resistance seen (only examined in one trial). No trial showed a significant harmful effect from antibiotic prophylaxis.
Comments	Heterogeneity of studies with respect to patient population, SDD regimen used and outcome definitions. Methodological quality of trials independently assessed by two authors. Data from 25/36 RCTs analysed on intention to treat. Unpublished studies included, decreasing risk of publication bias.

Study 5: 2005 Silvestri L	Impact of selective decontamination of the digestive tract on fungal carriage and infection: systematic review of randomized controlled trials.
Inclusion criteria	Included all RCTs that compared oropharyngeal and/or intestinal administration of antifungals amphotericin B or nystatin as part of SDD, with no treatment in the controls. No language restriction. All trials, published and unpublished, in unselected and selected critically ill patients were considered. Exclusion criteria: Studies which did not test enteral antifungals and in which both arms received antifungal prophylaxis. 42 RCTs included; 6075 critically ill patients.
Measurements	Outcome measures: Patients with fungal carriage, fungal infection and fungaemia.
Results	Enteral antifungals significantly reduced fungal carriage (OR 0.32, 95% CI 0.19-0.53) and overall fungal infections (OR 0.30, 95% CI 0.17-0.53). Fungaemia was not significantly reduced by the treatment group (OR 0.89, 95% CI 0.16-4.95) because the incidence in the control group was very low.
Comments	Included paediatric studies. Unpublished studies included, decreasing risk of publication bias. Methodological quality of trials independently assessed by three authors.

Study 6: 2007 Silvestri L et al	Selective decontamination of the digestive tract reduces bloodstream infections and mortality in critically ill patients: a systematic review of randomized controlled trials.
Inclusion criteria	Included all RCTs that compared oropharyngeal and/or intestinal administration of antibiotics as part of SDD protocol, with or without a parenteral component, with no treatment or placebo in the controls. No language restriction. Exclusion criteria: Studies in neutropenic patients, non-randomized studies, double publications, both arms received SDD but received another drug or endpoint not infection. 51 RCTs included; 8065 patients (4079 SDD, 3986 controls).
Measurements	Outcome measures: patients with bloodstream infection, causative micro-organisms and total mortality.
Results	SDD significantly reduced overall bloodstream infections (OR 0.73, 95% CI 0.59-0.90, p=0.0036), G-ve bloodstream infections (OR 0.39, 95% CI 0.24-0.63, p<0.001) and overall mortality (OR 0.80, 95% CI 0.69-0.94, p=0.0064). SDD did not significantly affect G+ve bloodstream infections (OR 1.06, 95% CI 0.77-1.47).
Comments	Unpublished studies included, decreasing risk of publication bias. Methodological quality of trials independently assessed by three authors. Four trials performed in paediatric intensive care units.

Study 7: 2008 Silvestri L	Impact of selective decontamination of the digestive tract on carriage and infection due to Gram-negative and Gram-positive bacteria. Systematic review of randomized controlled trials.
Inclusion criteria	All published and unpublished trials in unselected and selected critically ill patients considered. No language restriction. Exclusion criteria: Studies in neutropenic patients, non-randomized studies, double publications, both arms received SDD but received another drug, or endpoint not infection. 54 RCTs included; 9473 patients (4672 SDD, 4801 controls).
Measurements	Outcome measures: Carriage and severe infection due to G-ve and G+ve bacteria.
Results	SDD significantly reduced oropharyngeal carriage (OR 0.13, 95% CI 0.07-0.23), rectal carriage (OR 0.15, 95% CI 0.07-0.31), overall infection (OR 0.17, 95% CI 0.10-0.28), lower respiratory tract infection (OR 0.11, 95% CI 0.06-0.20) and bloodstream infection (OR 0.35, 95% CI0.21-0.67) due to G-ve bacteria. Reduction in G+ve carriage was not significant. G+ve lower airway infections were significantly reduced (OR 0.52, 95% CI 0.34-0.78). G+ve bloodstream infections were not significantly increased (OR 1.03, 95% CI 0.75-1.41). Other findings: The use of parenteral and enteral antimicrobials was superior to enteral antimicrobials alone in reducing carriage and severe infection from G-ve bacteria.
Comments	Methodological quality of trials independently assessed by three authors. May have been under-reporting of outcome measures as majority of RCTs included were not designed to assess these outcomes as primary endpoints. Four trials performed in paediatric intensive care units. Heterogeneity in results for each outcome tested for but not significant. Unpublished studies included, decreasing risk of publication bias. MRSA and VRE endemic in the ICUs of nine of the RCTs.

Study 8: 2009 Silvestri L	Survival benefit of the full selective digestive decontamination regimen.
Inclusion criteria	All RCTs from 1976-2007 comparing the full protocol SDD (parenteral plus enteral antimicrobials) with no treatment or placebo. No language restriction. Exclusion criteria: Studies that included neutropenic, stem cell and bone marrow transplant patients, double publications, and studies in which both arms received SDD (either parenteral or enteral, or both). 21 RCTs included; 4902 patients.
Measurements	Objectives: To assess the impact of the full SDD regimen (parenteral and enteral antimicrobials) on overall mortality, mortality attributable to infection, and early and late mortality.
Results	Overall mortality was significantly reduced (OR 0.71, 95% CI 0.61-0.82, p<0.001). There was a non-significant reduction in infection-related mortality (6 RCTs; OR 0.40, 95% CI 0.10-1.59, p=0.19) and early mortality (4 RCTs; OR 0.64, 95% CI 0.34-1.19, p=0.16), and a significant reduction in late mortality (5 RCTs; OR 0.56, 95% CI 0.40-0.77, p<0.001). The subgroup analysis showed a significant mortality reduction in successfully decontaminated patients (OR 0.58, 95% CI 0.45-0.77, p<0.001), and when parenteral and enteral antimicrobials were administered to every patient receiving treatment in the ICU (OR 0.59, 95% CI 0.42-0.82, p<0 .001).
Comments	Methodological quality of trials independently assessed by two authors.

Study 9: 2009 Liberati A	Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care.
Inclusion criteria	RCTs of antibiotic prophylaxis for respiratory tract infections and deaths among ICU patients. Exclusion criteria: Studies based on pre-selected groups of patients or where >50% of patients did not undergo mechanical ventilation for > 48 hours. 36 RCTs included; 6914 patients.
Measurements	Objectives: To assess the effects of prophylactic antibiotic regimens such as SDD on prevention of respiratory tract infections and overall mortality in adults receiving intensive care.
Results	In trials comparing a combination of enteral and systemic antibiotics there was a significant reduction in both respiratory tract infections (16 studies; OR 0.28, 95% CI 0.20-0.38) and total mortality (17 studies; OR 0.75, 95% CI 0.65-0.87) in the treated group. In trials comparing enteral antimicrobials alone or enteral plus systemic vs systemic alone, there was a significant reduction in respiratory tract infections (17 studies; OR 0.44, 95% CI 0.31-0.63) but not in total mortality (19 studies; OR 0.97, 95% CI 0.82-1.16) in the treated group.
Comments	Methodological quality of trials independently assessed by two authors.

Study 10: 2010 Silvestri L	Selective decontamination of the digestive tract reduces multiple organ failure and mortality in critically ill patients: systematic review of randomized controlled trials.
Inclusion criteria	All randomized trials comparing both oropharyngeal and intestinal administration of antibiotics in selective decontamination of the digestive tract with or without a parenteral component, with placebo or standard therapy used in the controls. No language restriction. Exclusion criteria: RCTs including neutropenic, stem cell and bone marrow transplantation patients, duplicate publications, and studies in which both arms received SDD. 7 RCTs included; 1270 patients
Measurements	Outcome measures: to examine the impact of selective decontamination of the digestive tract (SDD) on multiple organ dysfunction syndrome (MODS).
Results	SDD using parenteral and enteral antimicrobials reduces the number of patients with multiple organ dysfunction syndrome (OR 0.50, 95% CI 0.34-0.74). Mortality was not significantly reduced (OR 0.82, 95% CI 0.51-1.32) probably due to the small sample size (1,270 patients).
Comments	Methodology quality of trials independently assessed by two authors. One RCT performed in a paediatric intensive care unit.

Study 11: 2010 Petros A et al	Impact of selective decontamination of the digestive tract on morbidity and mortality in critically ill children: systematic review and meta –analysis of randomized controlled trials.
Inclusion criteria	All randomized trials in paediatrics comparing enteral administration of antibiotics of SDD (oropharyngeal, intestinal, or both), with or without a parenteral component, with no treatment or placebo in the controls. No language restriction. Exclusion criteria: non-randomized studies or studies with inappropriate design; double publications or studies including data extracted from main publication; both study arms received SDD; studies including neutropenic, stem cell and bone marrow transplant patients. 4 RCTs included; 335 patients
Measurements	The primary end point was the number of children who acquired pneumonia. Secondary end points were number of infections and overall mortality.
Results	There was a significant reduction in the incidence of pneumonia with SDD (OR 0.31, 95% CI 0.11-0.97). SDD had no impact on general infection rates (OR 0.34, 95% CI 0.05-2.18) and demonstrated a non-significant reduction in mortality (OR 1.18, 95% CI 0.50-2.76), probably due to the small sample size.
Comments	Methodology quality of trials independently assessed by three authors. All RCTs were performed in paediatric patients.

Table 3.5 – Detailed description of the four paediatric RCTs of SDD currently reported in the literature.

Study 1 Zobel G 1991	Reduction of colonization and infection rate during paediatric intensive care by selective decontamination of the digestive tract.
Intervention	Prospective randomized controlled trial. Treatment group received topical oral paste/gel containing poylmyxin E 3%, gentamicin 2% and amphotericin B 2% four times daily; enteral solution containing polymyxin E 100mg, gentamicin 80mg, amphotericin B 500mg and 10ml sodium chloride 0.9% four times daily (neonates: 1ml, infants: 2ml, 1-4 years: 3ml, 5-8 years: 4ml, >8 years: 5ml); and iv cefotaxime 100mg/kg three times daily. Control group received either perioperative antibiotic prophylaxis with cefuroxime or antibiotic therapy according to clinical or microbiological evidence of infection.
Inclusion criteria:	Critically ill paediatric patients endotracheally intubated and mechanically ventilated requiring intensive care for at least 4 days. n = 50 (25 treatment, 25 control).
Endpoints	Primary endpoint: The effect on colonisation and infection rates
Outcomes	Primary endpoint: Colonisation with Gram-negative micro-organisms and yeasts in the oropharynx and digestive and respiratory tracts increased rapidly in up to 52% of patients in the control group vs no colonisation in the treatment group ($p<0.01$). Rate of acquired secondary infections was 36% in the control group vs 8% in the treatment group ($p<0.025$). Other: No significant difference between the groups in the duration of intensive care, mechanical ventilation or mortality rate. Serum gentamicin concentrations were 1.5 ± 0.18mg/L.

Study 2 Ruza F 1998	Prevention of nosocomial infection in a paediatric intensive care unit (PICU) through the use of selective digestive decontamination.
Intervention:	Prospective randomized controlled trial. Treatment group received colistimethate (colistin) 50000units/kg (max 1500000units) qds, tobramycin 2.5mg/kg (max 75mg) qds and nystatin 25000units/kg (max 750000units) qds orally or via nasogastric tube. All patients undergoing mechanical ventilation or who were immunosupressed received oropharyngeal decontamination with hexitidine 0.5mg/ml every 6-8 hours.
Inclusion criteria:	Patients 1m – 14y who underwent some form of invasive instrumentation (mechanical ventilation, vascular cannulation, ICP monitoring, thoracic or intra-abdominal drainage, bladder catheterisation, peritoneal dialysis, parenteral nutrition etc) who presented in a neurological coma defined by a GCS of ≤10, requiring a stay in PICU of 3 or more days. n = 244 (116 treatment, 110 control, 18 withdrawn due to protocol violation).
Endpoints	Primary endpoint: Incidence of nosocomial infection Secondary endpoints: Use of antibiotics, length of stay and mortality.
Outcomes	Primary endpoint: Univariant analysis: No significant reduction in incidence of nosocomial infections with SDD Multivariant analysis: SDD acted as a protective factor for >90% of the sample with respect to respiratory and urinary tract infections, reducing the risk to 1/5 (odds ratio: 0.21) and 1/3 (odds ratio: 0.33), respectively. Secondary endpoints: Univariant analysis: No significant reduction in antibiotic use, length of stay or mortality with SDD.

Study 3 Smith SD 1993	Selective decontamination in paediatric liver transplants. A randomized prospective study.
Intervention:	Prospective randomized controlled trial. Treatment group received polymyxin E (<5years: 25mg; 5-12years: 50mg), tobramycin (<5years:10mg; 5-12years: 40mg) and amphotericin B (<5years:100mg, 5-12years: 250mg) qds via nasogastric tube as well as by oropharyngeal swab (methylcellulose paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B), continued only until feeding resumed, plus perioperative parenteral antibiotics (cefotaxime 100mg/kg/day and ampicillin 100mg/kg/day). Control group received perioperative parenteral antibiotics only (cefotaxime 100mg/kg/day and ampicillin 100mg/kg/day).
Inclusion criteria:	First-time orthotopic liver transplant recipients. Exclusion criteria: Failure to institute SDD immediately after admission to the ICU or repeat liver transplantation. n = 36 (18 treatment, 18 control)
Endpoints	Primary endpoint: Post-operative infections Secondary endpoints: Length of stay in ICU, total length of hospital stay, mortality.
Outcomes	Primary endpoint: There were significantly fewer patients with Gram-negative infections in the treatment group (8% vs 36%, $p<0.001$), as well as a significant reduction in aerobic Gram-negative flora in the stool ($p<0.05$) which returned to baseline by 3 weeks. Gram-positive and anaerobic organisms were unaffected. Secondary endpoints: ICU length of stay, total hospital length of stay and mortality were not significantly different between the two groups. Other: Mild diarrhoea was present in 6 of 18 patients receiving SDD.

Study 4 Barret JP 2001	Selective decontamination of the digestive tract in severely burned paediatric patients
Intervention:	Prospective randomized double-blind controlled trial. Treatment group received a suspension of poylmyxin E (100mg), tobramycin (100mg) and amphotericin B (500mg) via nasogastric tube four times a day. Placebo group received a control solution consisting of isotonic physiologic solution (Ringers lactate).
Inclusion criteria:	Severely burned paediatric patients between the ages of 0-18years, with full thickness burns over a 30% total body surface area, admitted within 5 days from the injury, without evidence of sepsis or organ failure. n = 23 (11 treatment, 12 placebo)
Endpoints	Primary endpoint: Bacterial colonisation of the digestive tract and burn wounds and the incidence of nosocomial infections and septic complications. Secondary endpoints: Serum levels of IL-1β, IL-6, IL-10 and TNF-α; episodes of diarrhea.
Outcomes	Primary endpoint: Colonisation rates of burn wounds, sputum, nasogastric aspirates and faeces were similar. Pneumonia, sepsis and other complications had similar incidences in both groups. Secondary endpoints: Serum levels of all cytokines studied were comparable in both groups. Patients in the treatment group had a significantly higher incidence of diarrhea (p=0.003).

Table 3.6 - Paediatric dosage regimen for the enteral and topical SDD components (Kucers').

Over 12 years:	SDD Oral Gel Colistin oral liquid Tobramycin base oral liquid Amphotericin B oral liquid	Topically qds 100mg (3 million units) po/ng qds 80mg po/ng qds 500mg po/ng qds	To be administered 30 minutes before feeds and not with feeds. Treatment to be continued until the patient has been extubated or until discharge from the ICU.
5-12 years:	SDD Oral Gel Colistin oral liquid Tobramycin base oral liquid Amphotericin B oral liquid	Topically qds 50mg (1.5 million units) po/ng qds 40mg po/ng qds 250mg po/ng qds	
1-4 years:	SDD Oral Gel Colistin oral liquid Tobramycin base oral liquid Amphotericin B oral liquid	Topically qds 25mg (750000 units) po/ng qds 20mg po/ng qds 100mg po/ng qds	
<1year:	SDD Oral Gel Colistin oral liquid Tobramycin base oral liquid Amphotericin B oral liquid	Topically qds 25mg (750000 units) po/ng qds 20mg po/ng qds 100mg po/ng qds	

Abbreviations: po/ng: orally/nasogastrically; qds: four times daily; ICU: intensive care unit; SDD: Selective Digestive Decontamination

Table 3.7 - UK licensing status, presentation & cost of the enteral and topical SDD components.

Drug	Form	Strength	License Status	Cost	Additional Information
SDD Oral Gel	Oral Gel	colistin 2%, tobramycin 2%, amphotericin 2%	Unlicensed	£9.75 per 5g tube	Refrigerate. Shelf life: 28 days after manufacture.
Colistin	Oral liquid	100mg/ml (=3million units/ml)	Unlicensed	£42.37 per 30ml bottle	Refrigerate. Shelf life 6 months after date of manufacture, reduce to 4 weeks after opening.
Tobramycin	Oral liquid	80mg/ml (base)	Unlicensed	£50.98 per 60ml bottle	Refrigerate. Shelf life 24 months after date of manufacture, reduce to 4 weeks after opening.
Amphotericin B	Oral liquid	100mg/ml	Unlicensed	£75.25 per 50ml bottle	Refrigerate. Shelf life 6 months after date of manufacture, reduce to 4 weeks after opening.

Data on costs and storage obtained from direct enquiry to individual companies and accurate as at August 2010

Chapter 4

META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS IN PAEDIATRIC PATIENTS

Introduction

There is level 1A evidence that SDD reduces severe infections of lower airways and blood and mortality in critically ill adults. However, there are very few randomized control trials (RCTs) in critically ill children requiring treatment on a paediatric intensive care unit (PICU) and the sample size of the studies are relatively small. There are no meta-analyses of SDD in paediatrics.

Since the recent Dutch RCT on selective decontamination of the digestive tract (SDD) demonstrated a significant reduction in mortality in critically ill adults in intensive care (de Smet AM *NEJM* 2009) there has been a resurgence of interest in the value of SDD. There are now 64 RCTs and 11 meta-analyses demonstrating significant reduction in morbidity and more importantly mortality in ventilated patients in intensive care.

The use of SDD in paediatrics has been very limited in contrast to the adult experience. This is in partly due to the low rates of infection and mortality in the general paediatric population. The overall mortality rate in paediatric intensive care varies (Sands R) between 5-10% compared to 20-30% in adults. There are of course subgroups of children who are at greater risk of infections and also death that could benefit from the use of SDD.

A meta analysis was undertaken with the aim of examining the impact of selective decontamination of the digestive tract (SDD) on morbidity and mortality in critically ill children. MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, were searched for previous RCTs and then a meta analysis was undertaken comparing administration of enteral antimicrobials in SDD with or without a parenteral component, with placebo or standard therapy used in the

controls. Primary end point was the number of children who acquired pneumonia. Secondary end points were number of children with infections and overall mortality. Odds ratios were pooled with the random effect model.

Four RCTs including 335 patients were identified. Pneumonia was diagnosed in 5 of 170 patients (2.9%) for SDD and 16 of 165 patients (9.7%) for controls (odds ratio, 0.31; 95% confidence interval, 0.11-0.87; p=0.027). Overall mortality for SDD was 13 of 170 (6.7%) vs. control, 11 of 163 (7.6%) demonstrating a non-significant reduction in the odds ratio for death (OR 1.18; 95% confidence interval, 0.50-2.76; p = 0.70). In three studies (n=109), infection occurred in 10 of 54 (13%) patients on SDD and 24 of 55 (15.9%) in the controls (OR, 0.34; 95% confidence interval, 0.05-2.18; p=0.25). SDD significantly reduces the number of children who develop pneumonia.

The participants in this systematic review and meta-analysis include children up to the age of sixteen who receive selective decontamination of the digestive tract. The reason for undertaking the meta-analysis is to assess the four paediatric RCTs with respect to the primary endpoint of pneumonia, the secondary endpoint of overall infection and finally overall mortality from in RCTs.

Search Strategy

RCTs were obtained by searching Electronic databases EMBASE, MEDLINE, with no restriction on language, or gender. Search key words were SDD, selective decontamination of the digestive tract, selective bowel decontamination, gut decontamination. In addition the authors searched their personal archives and published meta-analyses on SDD.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were established before reviewing abstracts and articles. All randomized trials comparing enteral administration of the SDD antibiotics (oropharyngeal, intestinal, or both), with or without a parenteral component, with no treatment or placebo in the controls were included. RCTs with usable information by outcome were finally included in the meta-analysis.

Studies were excluded for the following reasons: (1) non-randomized studies or studies with inappropriate design; (2) double publications or studies including data extracted from main publication; (3) both study arms received SDD; (4) studies including neutropenic, stem cell and bone marrow transplant patients.

Extraction of outcome measures

Three investigators independently retrieved the published findings from each study and compared the sets of data. Any disagreement was resolved by discussion. The following data were sought for each study and recorded on standard collection sheets: specific antimicrobials used and routes; number of patients in each arm; number of patients with pneumonia, and infection; number of deaths.

Quality Assessment

The quality of each study was assessed with reference to a predefined list of seven criteria in a scoring system of 0-14, reported originally by Heyland et al (Heyland DK) and modified by Brazzi et al and Silvestri et al (Brazzi L). The criteria included randomization, study blinding, patient selection, population description, reproducibility, definitions of infection and carriage (Silvestri L *JHI* 2007). The assessment was made by three investigators.

Definitions

Pneumonia was defined based on the individual clinical and laboratory criteria employed by the authors of the selected RCTs, i.e. fever, increased volume and purulence of lower airway secretions, a culture positive for potential pathogens in high concentrations ($\geq 10^5$ quantitatively or ≥2+ semi-quantitatively) and the presence of a new or evolving pulmonary infiltrate on the chest x-ray (Ruiz M). All other infections were defined according to Center Disease Control (CDC) criteria (Garner JS).

Mortality was evaluated at hospital discharge if this information was provided, otherwise mortality in PICU was used (Liberati A Cochrane Database 2009).

Statistical Analysis

The primary endpoint was the number of children developing pneumonia during treatment with SDD. Secondary end points were overall infection and mortality. We planned *a priori* the following subgroup analysis of the three endpoints: (a) type of regimen used (parenteral plus enteral or enteral only); (b) randomization procedures (adequate or inadequate); (c) blinding of patients and caregivers to allocated treatment (blinded or unblinded). We hypothesised that the treatment effect would be lower with enteral only regimen, in adequate randomisation, and in blinded studies. Randomisation was adequate when patients were randomized by telephone or a central office. A study was blinded when both caregivers and outcome assessors were blinded.

Results are presented as odds ratio (OR) with 95% confidence intervals (CI) using the random effects model. The Cochran Q statistic for heterogeneity was used both for the outcome measures and through subgroup analyses. We considered heterogeneity to be significant if the P value was <0.10. I^2 was also evaluated using the formula 100% x (Q-df)/Q where Q is Cochran Q, and df the degree of freedom (number of studies -1). Negative values of I^2 are equal to 0%. I^2<30% indicates mild heterogeneity and 30-50% moderate and >50% severe heterogeneity. Computations were performed using the EasyMA software (Cucherat M).

Results

Search findings and characteristics of the studies

The preliminary search identified 152 potentially relevant studies (Figure 4.1). Of these studies, 88 were excluded: 64 studies were not randomized, 21 RCTs were double publications, and 3 RCTs used SDD in both arms. We identified 64 potentially appropriate RCTs of whom 60 were excluded because there were not performed in children (supplementary material). A final sample of 4 RCTs, which enrolled a total of 335 patients (170 SDD, 165 controls), was the basis for the systematic review and meta-analysis.

The four RCTs are described in detail in Table 4.1 (Zobel G; Smith SD; Ruza F; Barret JP). The trials include a varied population ranging from severely burned paediatric patients, to children in paediatric intensive care units, to children undergoing liver transplantation. Quality assessment for all trials resulted in a median score of 9.2 (range 8.4 –9.9). Zobel G et al achieved a score 10.3, Smith et al 9.7, Ruza et al 7.3 and Barret et al of 8.7. This compares well with previous quality assessment of all the SDD meta analyses of adult and paediatric data which resulted in a median score of 9.0 (IQR 8-11) (Silvestri L *JHI* 2007). Leclerc & Noizet undertook a systematic review of the four paediatric studies (Leclerc F).

Zobel and colleagues studied 50 children in a cardiac paediatric intensive care unit. SDD was given to 25 children in a prospective RCT following surgery in addition to the routine antibiotic regimen and 25 children were controls. During the study colonisation with Gram-negative microorganisms and yeasts in the oropharynx, and digestive and respiratory tracts increased up to 52% in the control group. There was no colonisation with these microorganisms in the treatment group. The rates of acquired secondary infections in the control and treatment groups were 36% and 8%, respectively ($p<0.025$). There were no differences in length of intensive care or

Table 4.1 General characteristics of randomized controlled trials of selective decontamination undertaken in children.

									Regimen			
									Enteral			
Author	**Year**	**Country**	**n**	**Blinding**	**Randomization**	**Endpoint**	**Outcome SDD vs C**	**Population**	**Parenteral**	**Aerobic Gram-Negative Bacilli**	**Yeasts**	**Site**
Zobel et al	1991	Austria	50	No	Adequate	Colonisation Infection rates	0% vs 52% 8% vs 36%	Cardiac surgery	Cefotaxime	P, T	A	O, I
Smith et al	1993	United States	36	No	Adequate	Infection rates LOS Mortality	11% vs 50% NS NS	Liver transplants	Cefotaxime/ ampicillin 2 arms	P, T	A	O,I
Ruza et al	1998	Spain	224	No	Inadequate	Infection rates LOS Mortality	NS NS NS	Invasive instrumentation on ICU	none	Col, T	Ny	-,I
Barret et al	2001	United States	23	Yes	Inadequate	Infection rates Cytokines	NS NS	Severe burns	Vancomycin amikacin piperacillin	P, T	A	-,I

SDD, elective decontamination of the digestive tract; C, control; LOS, length of stay; NS, not significant; ICU, intensive care unit; P, polymyxin; Col, colistin; T, Tobramycin; A, Amphotericin; Ny, Nystatin;O, oropharynx; I, Intestine.

mortality. The authors concluded that SDD produced a significant reduction of the colonisation rate with Gram-negative bacteria and yeasts in critically ill paediatric patients following cardiac surgery and needing intensive care for more than 3 days. SDD also significantly reduces the Gram-negative infection rate of the respiratory system. However, it did not alter ICU length of stay or mortality rate.

Smith and colleagues undertook the first prospective RCT of short-term SDD in children having orthotopic liver transplantation. Oral and nasogastric SDD, in addition to routine parenteral antibiotics, was given to 18 children having transplants and only routine parenteral antibiotics to the control group of 18. There was no difference in the group's demographics, intensive care or hospital length of stay. During the study, 14 Gram-negative infections (intra-abdominal abscess 7, septicemia 5, pneumonia 1, urinary tract 1) developed in the 36 patients studied. Mortality was not significantly different in the two groups. There were significantly fewer patients with Gram-negative infections in the SDD group: 3/18 patients (11%) vs. 11/18 patients (50%) in the control group ($p< 0.001$). There was also significant reduction in aerobic Gram-negative flora in the stool and pharynx. The authors concluded that short-term postoperative SDD significantly reduces Gram-negative infections in children having orthotopic liver transplantation.

In a prospective, randomized, non-blinded and controlled trial Ruza et al studied children aged 1 month to 14 years old, who had any manipulation or instrumentation such as mechanical ventilation, vascular cannulation, monitoring of intracranial pressure, thoracic or abdominal drainage, bladder catheterization, peritoneal dialysis, and/or presented a neurological coma during a greater than 3 day stay in a tertiary PICU (Ruza F). Over a 2 year period 226 children were included in the study, the treatment group comprised 116 patients and the control group, 110 patients. The treatment group was given colimicin, tobramycin and nystatin administered orally or via nasogastric tube. Using univariate analysis SDD did not significantly reduce the incidence of nosocomial infection, the length of stay, or mortality. However, using multivariate analysis SDD decreased the incidence of respiratory and urinary tract infections, reducing the risk of such infections to 1/5 and 1/3, respectively. Ruza and colleagues concluded that SDD was effective in controlling respiratory and urinary tract infections in children admitted to the PICU, but it did not reduce the incidence of

other types of nosocomial infection.

Finally, Barret et al studied 23 children with severe burns (Barret JP) (Table 4.1). Following randomisation SDD was given in a double-blinded manner to 11 children and 12 received placebo. Both groups received parenteral antibiotics, the SDD group also received oral and nasogastric enteral antibiotics including polymyxin E, tobramycin and amphotericin B. Demographics, hospital course, microbiology results, complications, infectious episodes, and serum levels of IL-1beta, IL-6, IL-10, and TNF-alpha were compared. There was a similar incidence of colonization rates to the wound, sputum, nasogastric aspirates, and faeces. The incidence of pneumonia, sepsis and other complications was also similar in both groups as were serum levels of all cytokines studied. The authors noted a significantly higher incidence of diarrhoea (p=0.003) in the children who received SDD. They concluded that SDD is not effective in decreasing bacterial colonisation and infectious episodes in severely burned paediatric patients.

Pneumonia

All four RCTs included 335 patients in total (Figure 4.2). Pneumonia occurred in 5 of 170 patients (2.9%) of those who received SDD and in 16 of 165 patients (9.7%) in the control group. This was a significant reduction in the incidence of pneumonia with SDD (OR 0.31; 95% CI, 0.11-0.87; p = 0.027). Heterogeneity was not observed ($\chi 2 = 2.51$, p = 0.47, $I^2 = 0$) (Table 4.2 and 4.3).

Infection

In three RCTs, including 109 children, infections of various origins were confirmed in 10 of 54 (13%) children on SDD and in 24 of 55 (15.9%) children in the control group. SDD had no impact on general infection rates, with no overall difference between the groups (OR, 0.34; 95% CI 0.05-2.18; p = 0.25) (Table 4.2 and 4.3).

Mortality

The impact of SDD on mortality was analysed in all four studies. Overall mortality for those who received SDD versus those who did not was 13 of 170 (6.7%) and 11 of 163 (7.6%), respectively, demonstrating a non-significant reduction in the odds of death (OR 1.18; 95% CI 0.50-2.76; p = 0.70) (Table 4.2 and 4.3).

Subgroup analysis

Subgroup analyses of type of SDD regimen, randomisation, and blinding are shown in Table 4.4. A significant impact on infections and pneumonia was found with the use of the full protocol of parenteral and enteral antimicrobials rather than solely enteral antimicrobials. A significant impact on pneumonia and overall infection was demonstrated when randomisation was adequate and in unblinded studies. The subgroup analyses for mortality were consistent with previous pooled results whether the intervention was parenteral/ enteral or enteral, whether the design was blinded or not, whether the randomisation process was adequate or not. The Q and I^2 tests for heterogeneity yielded non-significant results in all comparisons.

Discussion

There are very few paedaitric studies on the use of SDD in critically ill children. Although there has been a systematic review of the four studies (Leclerc F), this is the first meta-analysis of the currently available RCTs. The numbers of children included are relatively small which probably accounts for the lack of significant effect on mortality or overall infection. However, even with relatively few numbers there is still a significant reduction in pneumonia rates. Using a recognised assessment tool for quality of studies included in meta-analyses the four studies resulted in a very acceptable median value for quality of studies. Previous studies have demonstrated that the infection rate using SDD is very low over a five year period (Sarginson RE).

The finding of this meta analysis in paediatrics is that SDD does not significantly reduce overall infections, nor mortality. However, there is a significant impact of SDD on reduction of the incidence of pneumonia in critically ill children (OR 0.34 p=0.027).)Previous reports have demonstrated that the infection rate in children using SDD is very low over a four year period (Sarginson RE). Furthermore, on subgroup analysis, when the full SDD protocol of enteral plus parenteral antibiotics is used there is significant reduction in overall infections (OR 0.13 (0.04-0.40; p<0.001). However, this subgroup analysis has to be taken with considerable caution as it involves small numbers of patients. The enteral component of SDD when used alone does not have an impact.

All four paediatric RCTs used non-invasive techniques to diagnose pneumonia consisting of tracheal aspirate and/or sputum. Invasive diagnosis of pneumonia with protected specimen brush or brancheoalveolar lavage following bronchoscopy is associated with halving the diagnosis of pneumonia (Cook D). However, invasive management does not impact upon mortality (Muscedere J). So using non-invasive techniques in paediatric is a good surrogate measure of diagnosing pneumonia.

We raised the question fifteen years ago whether mortality or morbidity was the goal to measure quality outcomes against (Petros AJ). Debate has ensued and morbidity is certainly now recognised as a valuable endpoint, particularly when it improves quality of care for the patient. Given this acknowledgement, the question has to be asked whether withholding SDD from critically ill children is now ethically questionable given the extensive adult literature (Zandstra DF *CC* 2010) and now the beginnings of a paediatric evidence base albeit limited. The answer must surely be yes. If there is a technique or treatment that convincingly demonstrates a reduction in morbidity is it unethical to not use it ?

Demonstrating an overall survival benefit with SDD may be very hard to achieve in pediatrics as the numbers needed to treat are potentially very large given the low mortality rate in pediatric intensive care. A simple sample size calculation assuming a 5% mortality in the control group looking for a 15% reduction in mortality to 4.25% with a 10% Type 1 error or false positive rate and a 10% Type 2 false negative rate, would require a sample size in the order of 27,390 children.

Mechanical ventilation can be seen as a measure of disease severity, defining the need for complex intensive care. The recent control of hyperglycaemia in paediatric intensive care trial (CHiP) (Control of hyperglycaemia in paediaitric intensive care) used as the primary outcome the number of days alive and free from mechanical ventilation within the 30 days after trial entry. The concept of ventilator free days (Vedas) brings together these two outcomes. Schoenfeld et al (Schoenfeld DA) define ventilator free days (VFDs) as: VFD=0 if the child dies before 30 days; VDF=(30-x) if the child is successfully weaned from ventilator within 30 days (where x is the number of days on ventilator) or VFD=0 if the child is ventilated for 30 days or more. The use of organ failure free days to determine patient-related morbidity surrogate end-points in

paediatric trials has been supported by influential paediatric trialists in the current low mortality paediatric critical care environment (Curley M). Even for this surrogate marker 1,500 children were needed just to be adequately powered to demonstrate a difference of two ventilator free days. Death was considered an important outcome but the study was not powered to detect a difference in mortality.

Extrapolating from adult data into paediatric practice is generally considered inadvisable. However, even if the significant reduction in mortality in adults given SDD is to be ignored, the reduction in pneumonia, which parallels the adult observations, tantalizingly hints at the possibility of a potential reduction in mortality in paediatrics, if studies were to be carried out which were powered adequately with large enough total number of children. As this is unlikely to happen the potential benefit of a proven maneuver in adults is lost to the paediatric world rendering the paediatric population again therapeutic orphans. Until this happens the potential benefit of a proven maneuver in adults is lost to the pediatric world rendering the pediatric population again therapeutic orphans. It took almost six years from the early suggestions of using of inhaled nitric oxide (Bigatello LM) until to a number of RCTs characterized its benefits (Roberts JD Jr, Clark RH).

Although disparate and small, the four limited studies performed in children, allow a meta-analysis which clearly demonstrates a significant reduction in pneumonia rates. SDD significantly reduces the number of children who develop pneumonia. Barret et al could not demonstrate any treatment benefit from SDD in children with severe burns so at this stage SDD cannot be advocated in this patient population. Furthermore, there was no overall reduction in mortality, nor a reduction in overall infection rates, probably because of the small sample size.

However, on the evidence presented it may be worth considering the use of SDD in certain groups of vulnerable children, such as those with a high risk of mortality score or those undergoing solid organ transplantation, whilst awaiting evidence of any survival benefit from large multi centre randomized control trials ?

Table 4.2 – Descriptions of the four paediatric RCTs currently in the literature.

Study 1 1991 Zobel G et al	Reduction of colonization and infection rate during paediatric intensive care by selective decontamination of the digestive tract.
Intervention	Prospective randomized controlled trial. Treatment group received topical oral paste/gel containing polymyxin E 3%, gentamicin 2% and amphotericin B 2% four times daily; enteral solution containing polymyxin E 100mg, gentamicin 80mg, amphotericin B 500mg and 10ml sodium chloride 0.9% four times daily (neonates: 1ml, infants: 2ml, 1-4 years: 3ml, 5-8 years: 4ml, >8 years: 5ml); and iv cefotaxime 100mg/kg three times daily. Control group received either perioperative antibiotic prophylaxis with cefuroxime or antibiotic therapy according to clinical or microbiological evidence of infection.
Inclusion criteria:	Critically ill paediatric patients endotracheally intubated and mechanically ventilated requiring intensive care for at least 4 days. n = 50 (25 treatment, 25 control).
Endpoints	Primary endpoint: Colonisation and infection rates
Outcomes	Primary endpoint: Colonisation with Gram-negative micro-organisms and yeasts in the oropharynx and digestive and respiratory tracts increased rapidly in up to 52% of patients in the control group vs. no colonisation in the treatment group ($p<0.01$). Rate of acquired secondary infections was 36% in the control group vs. 8% in the treatment group ($p<0.025$). Other: No significant difference between the groups in the duration of intensive care, mechanical ventilation or mortality rate. Serum gentamicin concentrations were 1.3 ± 0.18mg/L.

Study 2 1993 Smith SD et al	Selective decontamination in paediatric liver transplants. A randomized prospective study.
Intervention:	Prospective randomized controlled trial. Treatment group received polymyxin E (<5years: 25mg; 5-12years: 50mg), tobramycin (<5years:10mg; 5-12years: 40mg) and amphotericin B (<5years:100mg, 5-12years: 250mg) qds via nasogastric tube as well as by oropharyngeal swab (methylcellulose paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B), continued only until feeding resumed, plus perioperative parenteral antibiotics (cefotaxime 100mg/kg/day and ampicillin 100mg/kg/day). Control group received perioperative parenteral antibiotics only (cefotaxime 100mg/kg/day and ampicillin 100mg/kg/day).
Inclusion criteria:	First-time orthotropic liver transplant recipients. Exclusion criteria: Failure to institute SDD immediately after admission to the ICU or repeat liver transplantation. n = 36 (18 treatment, 18 control)
Endpoints	Primary endpoint: Post-operative infections Secondary endpoints: Length of stay in ICU, total length of hospital stay, mortality.
Outcomes	Primary endpoint: There were significantly fewer patients with Gram-negative infections in the treatment group (8% vs. 36%, $p<0.001$), as well as a significant reduction in aerobic Gram-negative flora in the stool ($p<0.05$) which returned to baseline by 3 weeks. Gram-positive and anaerobic organisms were unaffected. Secondary endpoints: ICU length of stay, total hospital length of stay and mortality were not significantly different between the two groups. Other: Mild diarrhoea was present in 6 of 18 patients receiving SDD.

Study 3 1998 Ruza F et al	Prevention of nosocomial infection in a paediatric intensive care unit (PICU) through the use of selective digestive decontamination.
Intervention:	Prospective randomized controlled trial. Treatment group received colistimethate (colomycin) 50000units/kg (max 1500000units) qds, tobramycin 2.5mg/kg (max 75mg) qds and nystatin 25000units/kg (max 750000units) qds orally or via nasogastric tube. All patients undergoing mechanical ventilation or who were immunosupressed received oropharyngeal decontamination with hexitidine 0.5mg/ml every 6-8 hours.
Inclusion criteria:	Patients 1m – 14y who underwent some form of invasive instrumentation (mechanical ventilation, vascular cannulation, ICP monitoring, thoracic or intra-abdominal drainage, bladder catheterisation, peritoneal dialysis, parenteral nutrition etc) who presented in a neurological coma defined by a GCS of ≤10, requiring a stay in PICU of 3 or more days. n = 244 (116 treatment, 110 control, 18 withdrawn due to protocol violation).
Endpoints	Primary endpoint: Incidence of nosocomial infection Secondary endpoints: Use of antibiotics, length of stay and mortality.
Outcomes	Primary endpoint: Univariant analysis: No significant reduction in incidence of nosocomial infections with SDD Multivariant analysis: SDD acted as a protective factor for >90% of the sample with respect to respiratory and urinary tract infections, reducing the risk to 1/5 (odds ratio: 0.21) and 1/3 (odds ratio: 0.33), respectively. Secondary endpoints: Univariant analysis: No significant reduction in antibiotic use, length of stay or mortality with SDD.

Study 4 2001 Barret JP et al.	Selective decontamination of the digestive tract in severely burned paediatric patients
Intervention:	Prospective randomized double-blinded controlled trial. Treatment group received a suspension of poylmyxin E (100mg), tobramycin (100mg) and amphotericin B (500mg) via nasogastric tube four times a day. Placebo group received a control solution consisting of isotonic physiologic solution (Ringers lactate).
Inclusion criteria:	Severely burned paediatric patients between the ages of 0-18years, with full thickness burns over a 30% total body surface area, admitted within 5 days from the injury, without evidence of sepsis or organ failure. n = 23 (11 treatment, 12 placebo)
Endpoints	Primary endpoint: Bacterial colonisation of the digestive tract and burn wounds and the incidence of nosocomial infections and septic complications. Secondary endpoints: Serum levels of IL-1β, IL-6, IL-10 and TNF-α; episodes of diarrhoea.
Outcomes	Primary endpoint: Colonisation rates of burn wounds, sputum, nasogastric aspirates and faeces were similar. Pneumonia, sepsis and other complications had similar incidences in both groups. Secondary endpoints: Serum levels of all cytokines studied were comparable in both groups. Patients in the treatment group had a significantly higher incidence of diarrhoea (p=0.003).

Table 4.3

Data extracted from four randomized controlled trials of selective digestive decontamination in the paediatric population.

Author	Patients		Patients with infection		Patients with pneumonia		Mortality	
	SDD	C	SDD	C	SDD	C	SDD	C
Zobel	25	25	2	10	1	6	3	2
Smith	18	18	3	11*	0	2	2	3
Ruza	116	110	NA	NA	3	8	6	5
Barret	11	12	5	3	1	0	2	1

RCTs, randomized controlled trials; OR, odds ratio; CI, confidence interval; SDD, selective digestive decontamination; C control. ; NA, not available

*patients with Gram- negative infections.

Table 4.4

Meta-analysis of the impact of selective digestive decontamination on secondary endpoints.

Outcome	RCTs	N° of patients		N° of patients with outcome		OR (95 CI)	P	I^2
		SDD	C	SDD	C			
Pneumonia	4	170	165	5	16	0.31 (0.11-0.87)	0.027	0%
Infection	3	54	55	10	24	0.34 (0.05-2.18)	0.25	4.7%
Mortality	4	170	165	13	11	1.18 (0.50-2.76)	0.70	0%

RCTs, randomized controlled trials; OR, odds ratio; CI, confidence interval; SDD, selective digestive decontamination; C control. OR less than the unit favors treatment; OR above the unit favours controls. I^2 test for heterogeneity.

Table 4.5 Subgroup analysis of the impact of selective digestive decontamination on the endpoints of pneumonia, infection, and mortality.

Endpoints	N° RCTs	N° patients		N° events		OR (95% CI)	p
		SDD	C	SDD	C		
Pneumonia							
Parenteral plus enteral	2	43	43	1	8	0.14 (0.02-0.89)	0.037
Enteral only	2	127	122	4	8	0.65 (0.07-6.34)	0.71
Randomization adequate	2	43	43	1	8	0.14 (0.02-0.89)	0.037
Randomization inadequate	2	127	122	4	8	0.65 (0.07-6.34)	0.71
Blinded	1	11	12	1	0	5.97 (0.07-471.43)	NE
Not blinded	3	159	153	4	16	0.26 (0.09-0.76)	0.013
Infections							
Parenteral plus enteral	2	43	43	5	21	0.13 (0.04-0.40)	<0.001
Enteral only	1	11	12	5	3	2.50 (0.43-14.61)	NE
Randomization adequate	2	43	43	5	21	0.13 (0.04-0.40)	<0.001
Randomization inadequate	1	11	12	5	3	2.50 (0.43-14.61)	NE
Blinded	1	11	12	5	3	2.50 (0.43-14.61)	NE
Not blinded	2	43	43	5	21	0.13 (0.04-0.40)	<0.001
Mortality							
Parenteral plus enteral	2	43	43	5	5	1 (0.26-3.84)	1
Enteral only	2	127	122	8	6	1.32 (0.44-3.95)	0.62
Randomization adequate	2	43	43	5	5	1 (0.26-3.84)	1
Randomization inadequate	2	127	122	8	6	1.32 (0.44-3.95)	0.62
Blinded	1	11	12	2	1	2.44 (0.19-31-54)	NE
Not blinded	3	159	153	11	10	1.08 (0.44-2.66)	0.87

RCTs, randomized controlled trials; SDD, selective decontamination of the digestive tract; C, control; OR, odds ratio, CI, confidence interval; NE, not evaluated as only one study was included. The Q and I^2 tests for heterogeneity were not significant in all comparisons. OR <1 favors treatment; OR >1 favors controls.

Figure 4.1

Selection procedure for studies meeting the inclusion criteria.

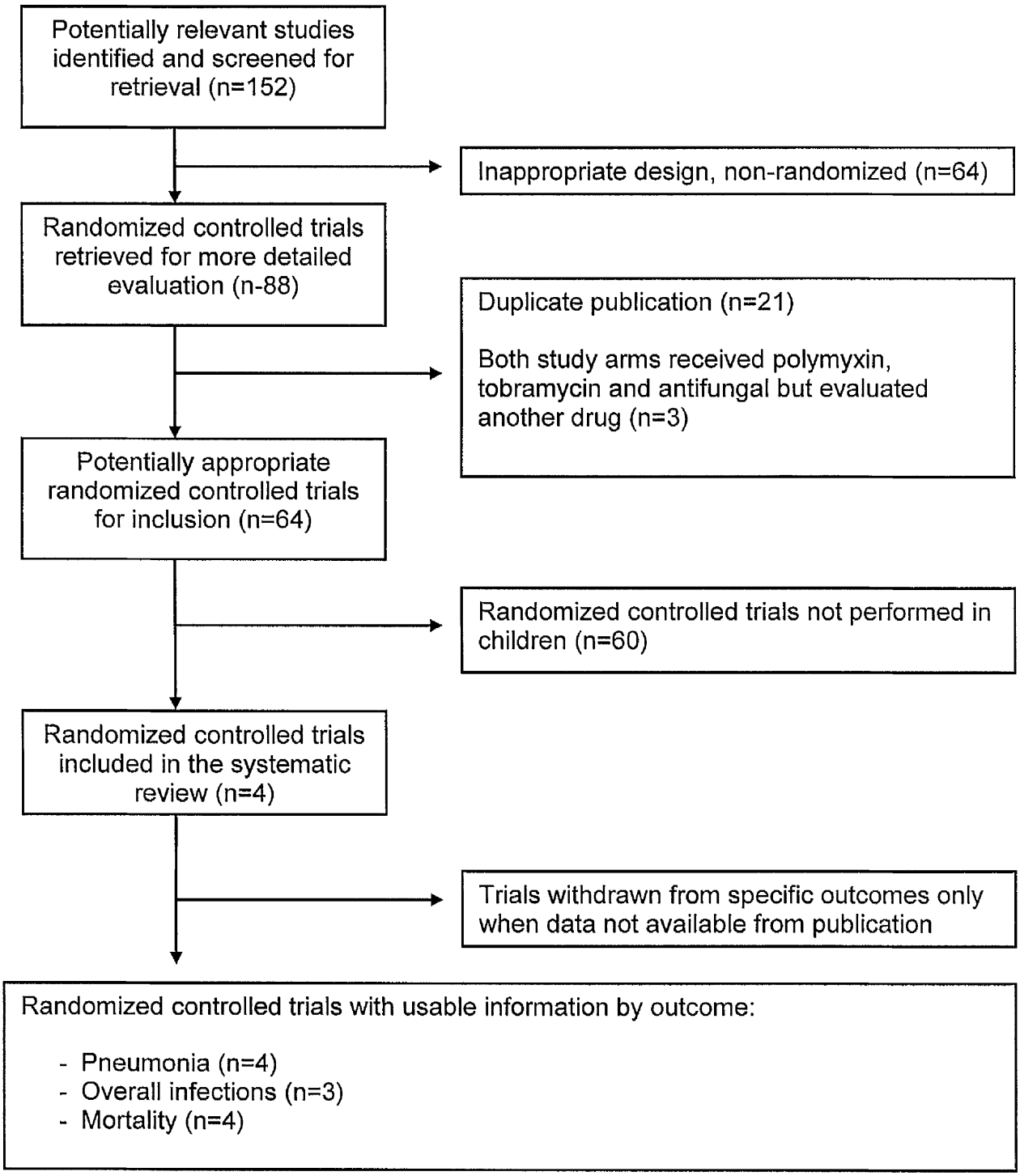
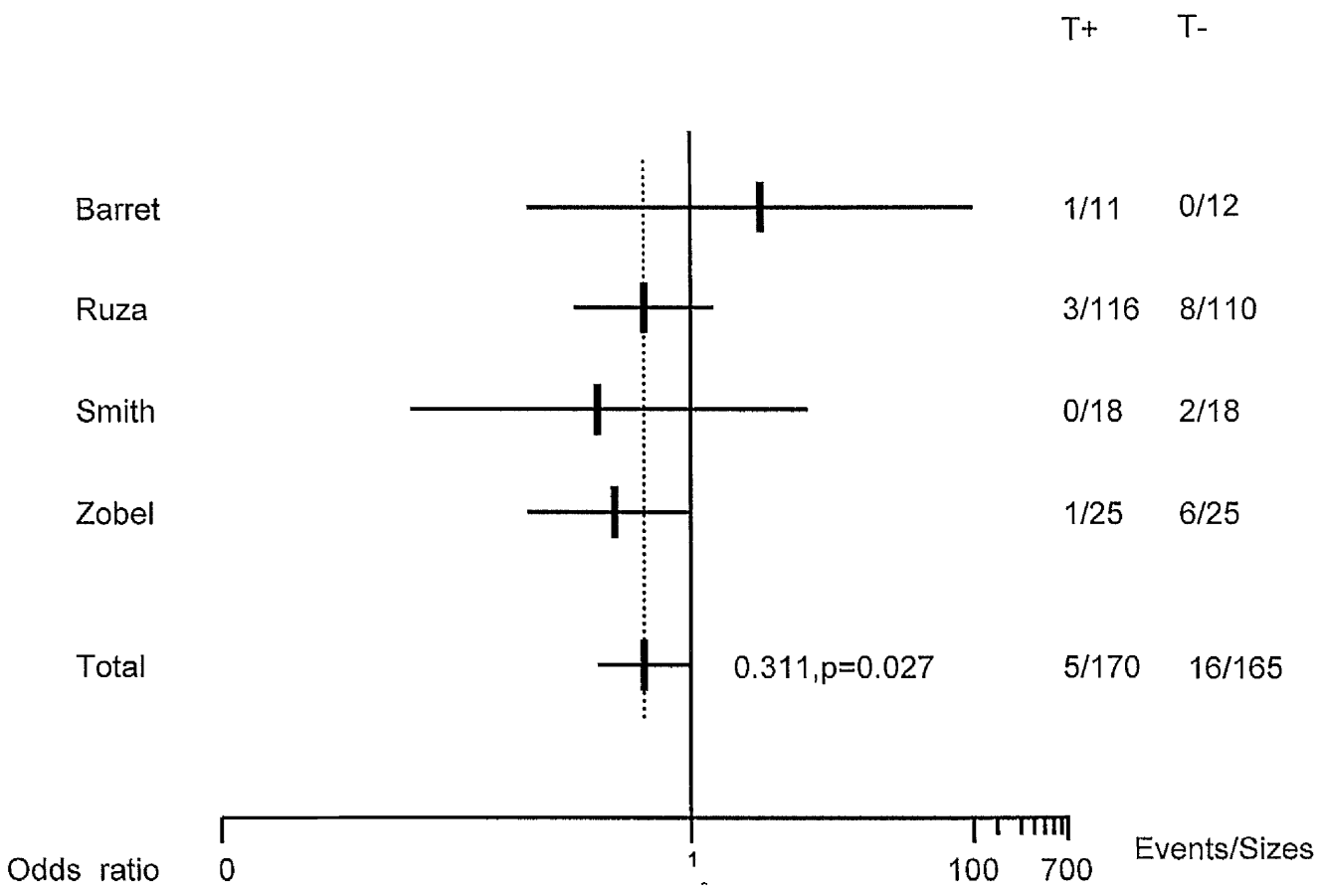


Figure 4.2

Effect of selective decontamination of the digestive tract on pneumonia in children.



Odds ratio <1 favours treatment; odds ratio > 1 favours control

T+, selective decontamination group; T-, control group

Chapter 5

MORTALITY RATES AND ADMISSION DIAGNOSES FOR CHILDREN ADMITTED TO PAEDIATRIC INTENSIVE CARE: A 5-YEAR DATASET

Magnitude of the problem

In this chapter the magnitude of the problem of mortality in PICU is explored. Using the PICANet database for admission between 2005-2009 various demographics and outcomes have been analysed and are presented, mortality rates are described and other relevant variables.

Sarginson reports that the overall mortality rate at AH was 5% for the year 2004. However, in a subset of 300 patients requiring PICU for >4 days the mortality increased to 10%. Brierley et al reports a mortality rate of 2/30 (6.6%) in PICU rising to 5/30 (16.6%) in hospital in severely septic children at GOSH. Sands reports a mortality rate of 5% overall over a 10 year period in their PICU. Overall morality rate in GOSH in 2007 was reported as 5.5% (Ramnarayan P)

Mortality rates vary according to disease condition. Watson suggests mortality from sepsis is 7% - our estimate of severe sepsis-associated deaths represents 7% of all deaths in children in 1995.

So mortality rates are higher for specific pathologies. Markovitz BP et al found in a group of 6693 children aged 0-17 years with severe sepsis, an overall mortality of 24% (Markovitz BP). They identified that age, hematologic-oncologic diagnosis, case volume, and use of steroids remained independent predictors of mortality in multivariable analysis.

Thorburn reported that his group found the mortality from pneumococcal sepsis was greater than that form meningococcal sepsis (Thorburn K). Eight (4.3%) children died from meningococcal sepsis. The study included 22 children with invasive pneumococcal disease (IPD), median age 14 months (interquartile range 3-52),

median Paediatric Index of Mortality (PIM) 0.051 (0.028-0.066), median length of PICU stay 8.5 days (4-13). Four patients died, three (13.5%) attributable to IPD.

Naghib et al also identified the relationship between illness severity and survival in children on PICU (Naghib S). The longer children stayed in PICU the higher their risk of mortality irrespective of initial cause. In their PICU, 4.4% of the children (116/2,607, equal gender, mean age 29 days) had a prolonged stay. Median (range) stay was 56 (28–546) days. These children accounted for 3% of total admissions and occupied 63% of total admission days. Mortality during admission for this group was five times higher (22%) than the average PICU mortality rate of 4.6%. Withdrawal or limitation of therapy preceded 70% of deaths.

The aim of this chapter is to explore the incidence of mortality in children requiring intensive care. The purpose of this is to determine whether any manoeuvre designed to reduce mortality could actually have a significant impact. If mortality rates are very low then it may not be possible to demonstrate an impact.

Methods

Data was obtained from the PICANet resource for the years 2004-2008 on all cause mortality. All twenty three PICUs in the UK report to PICANet on an annual basis. The data is anonymised and an annual report is produced by the Leeds group. Following formal request to the PICANet office, the data was sent in an excel spreadsheet (Microsoft Office 2007) and analysis of the demographic data and statistical analysis performed.

The PICANet data was interrogated and demographic data was extracted (Table 5.1). Admission and diagnostic data are presented as Read Codes (Table 5.2). Read codes are diagnoses coding system used in General Practice in the United Kingdom. It supports detailed clinical encoding of multiple patient phenomena including: occupation; social circumstances; ethnicity and religion; clinical signs, symptoms and observations; laboratory tests and results; diagnoses; diagnostic, therapeutic or surgical procedures performed and a variety of administrative items. It therefore includes but goes significantly beyond the bounds of a diagnosis coding

system. These diagnoses were sifted using Microsoft Access and the most frequent diagnoses for the major systems are presented in Table 5.3.

Results

Over the five year period 2004-2008, 83,863 children were admitted to 23 PICUs in the UK. Boys were more frequently admitted (56.5%) compared to girls (43.3%). The average age was 45.8 months (range 0-227). Not surprisingly, there was a seasonal variation in admission rates with highest numbers of admissions occurring between October and January. The average length of stay was 5.51 days (range 0-588) and 72.4% of all admission required mechanical ventilation. There were number of routes of admission to the PICU. The most common route of admission was an unplanned admission as an emergency from outside the Trust and accounted for 54.1% of all admissions; only 54% of those children were intubated on admission. Planned admission following elective surgery accounted for 33.6% admissions and of those 66.6% were intubated and needed mechanical ventilation.

Within the Read codes, which are defined as A-Z there are numerous sub classifications defining virtually every medical diagnosis known. Table 5.4 broadly describes the distribution of cases for the major codes. In certain common conditions the individual code has been identified and highlighted with the relevant clinical diagnosis. For example, in category H the code H0615 for acute bronchiolitis due to respiratory syncitial virus reports 1692 incidences during the five year period. There were of course more cases than this but they will have been reported differently, perhaps as pneumonia or just bronchiolitis with no cause and they will have been allocated a different code, for instance the code XSDOK reports just bronchiolitis. Similarly, there are no reports of any diseases which fall into category O of the Read coding. Code P describes the cardiovascular system and hence there are a number of reports.

Table 5.1 Demographic data of admission 2004-2008.

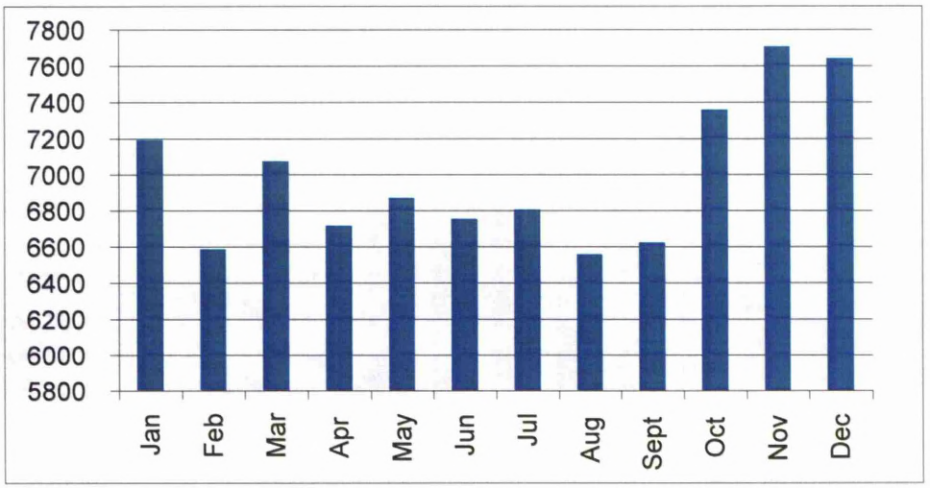
Total number of admissions 83,863

Gender distribution

Male	47,424	56.5%
Female	36,379	43.4%
Unrecorded/unknown	60	0.07%

Average Age 45.8 months (SD 60.4m) min 0– max 227 months

Annual distribution of admissions



Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
7188	6585	7071	6714	6868	6753	6805	6555	6623	7356	7705	7640

Average length of stay 5.51 days (SD 14.98) Min 0 – Max 588

Reasons for admission and intubation rate

Intubation		NO	YES	%
Planned -following surgery	28192	4925	18775	66.6
Unplanned -following surgery	4156	893	1932	46.5
Unplanned other	45358	11214	24545	54.1
Planned other	5997	1669	2485	41.4
Unknown	94	25	32	34.0

Rate of Mechanical ventilation 60742 (72.4%)

Table 5.2

Most commonly returned Read Codes for primary reason for admission 2004-2008. Every medical diagnostic condition has been given a Read code (Bentley T).

Read Code	Incidence	Sub-category	Incidence	Description
A	1678	A362	1031	
B	839	B640	232	
C	976	C101	424	
D	351	D1062	106	
		D113	109	
E	25			
F	2106	F001	249	
		F2512	287	
G	1364	G55	250	
H	6625	H47	496	
		H0615	1692	Acute bronchiolitis due to respiratory syncytial virus
		H061	1154	
		H33	547	
I	0	-		
J	1166	J500	161	
K	328	K04	177	
L	7			
M	79			
N	360	N373z	245	
O	1			
P	16539	P51	1643	Discordant ventriculoarterial connection
		P510	513	Total great vessel transposition
		P511	555	Double outlet right ventricle
		P52	1931	Tetralogy of Fallot
		P54	2479	Ventricular septal defect
		P67	1333	Hypoplastic left heart syndrome
		P70	1024	Patent ductus arteriosus
		P71	1271	Interrupted aortic arch
Q	1401	Q464	613	Neonatal necrotising enterocolitis
R	45			
S	900			
T	9			
U	64			
V	0			
W	0			
X	48097	XSDOK	1312	Bronchiolitis
		XM09V	1985	Respiratory failure
		X007B	1731	Status epilepticus
		X100E	1236	Pneumonia
		X70D3	1007	Acquired scoliosis
		X70VZ	1497	Sepsis
		X77wc	1352	
		X77vY	1127	Atrial septal defect
		XA003	1169	Injury of head region
Y	38			
Z	54			

Table 5.3

Most commonly returned Read Codes for primary reason for admission 2004-2008. Every medical diagnostic condition has been given a Read code (Bentley T).

Read Code	Incidence	Sub-category	Incidence	Description
A	1678	A362	1031	
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		F2512	287	
G	1364	G55	250	
H	6625	H47	496	
		H0615	1692	Acute bronchiolitis due to respiratory syncytial virus
		H061	1154	
		H33	547	
I	0	-		
J	1166	J500	161	
K	328	K04	177	
L	7			
M	79			
N	360	N373z	245	
O	1			
P	16539	P51	1643	Discordant ventriculoarterial connection
		P510	513	Total great vessel transposition
		P511	555	Double outlet right ventricle
		P52	1931	Tetralogy of Fallot
		P54	2479	Ventricular septal defect
		P67	1333	Hypoplastic left heart syndrome
		P70	1024	Patent ductus arteriosus
		P71	1271	Interrupted aortic arch
Q	1401	Q464	613	Neonatal necrotising enterocolitis
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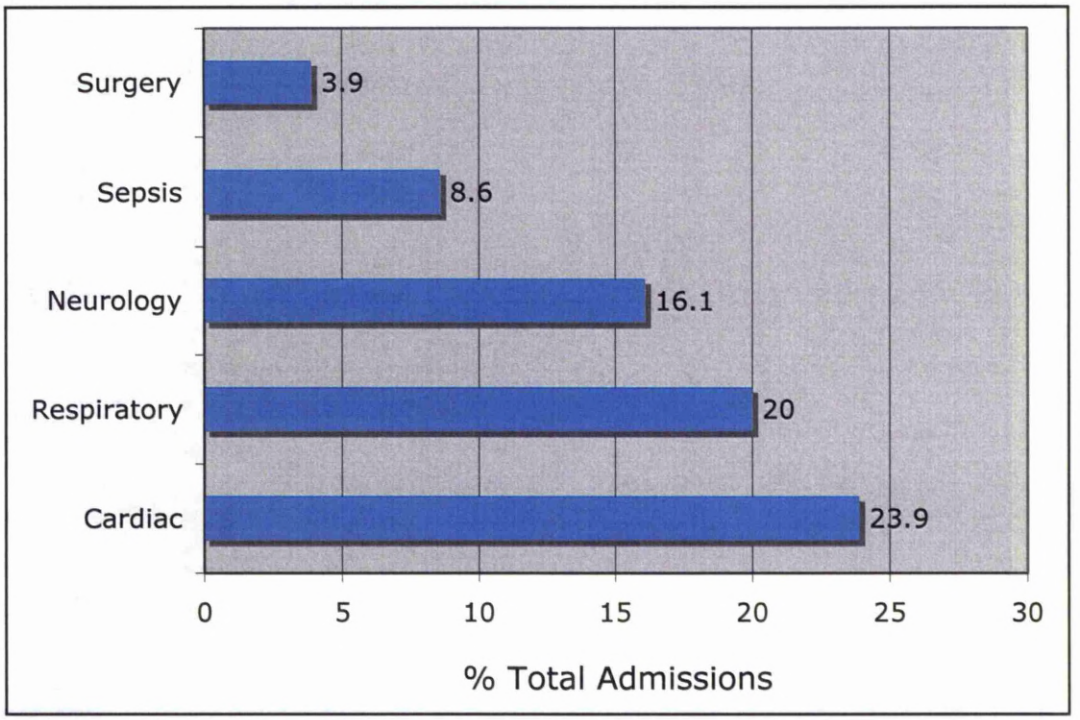
U	64			
V	0			
W	0			
X	48097	XSDOK	1312	Bronchiolitis
		XM09V	1985	Respiratory failure
		X007B	1731	Status epilepticus
		X100E	1236	Pneumonia
		X70D3	1007	Acquired scoliosis
		X70VZ	1497	Sepsis
		X77wc	1352	
		X77vY	1127	Atrial septal defect
		XA003	1169	Injury of head region
Y	38			
Z	54			

Table 5.3

Top diagnoses for admission for major specialities over the 5 year period.



Sifting the PICANet database reveals the systems which present with illness and the most common diagnoses within these groups. Table 5.4 shows the twenty most common reasons for admission to PICU. The most common reason for admission is cardiac and repair of ventricular septal defect the most common cardiac defect. The next most common reason for admission is due to respiratory failure, then neurology and sepsis with surgery contributing only a small percentage of admissions. Looking at individual systems the most frequent diagnoses for admission are listed in Table 5.5.

Mortality Rates

Mortality rates in the UK for the five year period 2004-2008 were 5.3%, 4.9%, 5.3%, 4.8% and 4.4% respectively and are shown in Table 6.1. It can be seen that for this period the average rate is 4.85%. The average PIM score (see page 132) was

0.0579 and the average SMR (see page 125) for the whole country was 0.84. As the PIM score increases the mortality does too. Those who survived had a SMR of 0.99 and those who died had an SMR of 0.24. With a PIM of <0.05 the average national mortality rate (Table 6.3b) was 2.048%; PIM 0.5-1.0 it was 7.85%; PIM 1.0-15 it was 9.2%; PIM 1.5-2.0 it was 13.11%; PIM 2.0-2.5 19%; PIM 2.5-3.0 20.4%; 3.0-4.0 26.0% and greater than 4.0 it was 58% (Table 6.3).

The mortality rates and SMRs (see page 133) for Liverpool and the National average were not significantly different for any of the PIM ranges except for PIM 3.0-4.0 when significant difference is seen both in mortality rate and SMR for the 5 year period. Krueger found, in a post-hoc analysis, a similar effect in adults for mid-range Acute Physiology and Chronic Health Evaluation (APACHE)-II scores between 20-29 on admission (Kruger WA).

Conclusions

The use of SDD in the whole paediatric ICU population is unlikely to have any significant effect on mortality of 5%. It may be more beneficial to target the higher risk groups. Those children with high PIM2 scores, or specific pathology groups i.e. haematologic-oncologic, those who require steroids, those with severe sepsis. Even targeting these heterogeneous groups may not demonstrate a positive effect as the numbers needed to show significance may still be too large.

The other option to reducing mortality is to try and influence morbidity. The most obvious area to try and influence is that of resistance. Using SDD may reduce the resistance profile and may reduce the requirement for long-term antibiotic usage or broad spectrum antibiotics. Also by controlling overgrowth other features of super infection may be avoided such as line infection and ventilator associated pneumonias. All these morbidities have certainly been impacted by SDD in the adult world.

There is an impact on mortality using SDD in paediatric intensive care but only in the mid-range SMR, and not overall. Extremes of scores are not sensitive enough to detect a survival benefit by any intervention. Those with low scores are likely to

survive anyway and would need large sample size for any trail to show any benefit. And those with very high scores are almost invariably going to die whatever intervention is used.

Table 5.4

Incidence of top 20 most common primary diagnoses requiring admission to PICU.

	Total Number	%
Ventricular septal defect	2479	3.0
Respiratory failure	1985	2.4
Tetralogy of Fallot	1931	2.3
Status epilepticus	1731	2.1
Acute bronchiolitis due to respiratory syncytial virus	1692	2.0
Discordant ventriculoarterial connection	1643	2.0
Sepsis	1497	1.8
Atrioventricular septal defect & common atriovent junction	1352	1.6
Hypoplastic left heart syndrome	1333	1.6
Bronchiolitis	1312	1.6
Aortic coarctation	1251	1.5
Pneumonia	1236	1.5
Injury of head region	1169	1.4
Acute bronchiolitis	1154	1.4
Atrial septal defect	1127	1.3
Meningococcal septicaemia	1031	1.2
Patent ductus arteriosus	1024	1.2
Acquired scoliosis	1007	1.2
Acute lower respiratory tract infection	843	1.0

Table 5.5

Most frequent diagnoses within individual systems, requiring PICU admission.

Cardiac	Incidence	% of total
Ventricular septal defect	2479	3.0
Tetralogy of Fallot	1931	2.3
Discordant ventriculoarterial connection	1643	2.0
Atrioventricular septal defect & common atriovent junction	1352	1.6
Hypoplastic left heart syndrome	1333	1.6
Aortic coarctation	1251	1.5
Atrial septal defect	1127	1.3
Patent ductus arteriosus	1024	1.2
Congenital heart disease	567	0.7
Double outlet right ventricle	555	0.7
Total great vessel transposition	513	0.6
Aortic stenosis	493	0.6
Pulmonary atresia with ventricular septal defect	483	0.6
Persistent truncus arteriosus	338	0.4
Subaortic stenosis	284	0.3
Pulmonary valve stenosis	279	0.3
Tricuspid atresia	268	0.3
Cyanotic congenital heart disease NOS	262	0.3
Coarctation of aorta NOS	260	0.3
Cardiomyopathy	250	0.3

Respiratory	Incidence	% of total
Respiratory failure	1985	2.4
Acute bronchiolitis due to respiratory syncytial virus	1692	2.0
Bronchiolitis	1312	1.6
Pneumonia	1236	1.5
Acute bronchiolitis	1154	1.4
Acute lower respiratory tract infection	843	1.0
Respiratory distress	690	0.8
Asthma	547	0.7
Status asthmaticus	516	0.6
Aspiration pneumonitis	496	0.6

Neurology	Incidence	% of total
Status epilepticus	1731	2.1
Injury of head region	1169	1.4
Febrile convulsion	568	0.7
Intracranial tumour	555	0.7
Head injury NOS	445	0.5
Seizure	397	0.5
Meningitis	358	0.4
Hydrocephalus	342	0.4
Isolated seizures	316	0.4
Epileptic seizures - clonic	287	0.3

Surgery	Incidence	% of total
Neonatal necrotising enterocolitis	613	0.7
Gastroschisis	597	0.7
Gastro-oesophageal reflux disease	563	0.7
Kyphoscoliosis or scoliosis NOS	245	0.3
Obstruction of intestine	240	0.3
Hirschsprung's disease	233	0.3
Oesophageal atresia with tracheo-oesophageal fistula	230	0.3
Tracheo-oesophageal fistula	209	0.3
Cleft palate	204	0.2
Idiopathic scoliosis	202	0.2
Diaphragmatic hernia	189	0.2
Adolescent idiopathic scoliosis	171	0.2
Intussusception	161	0.2
Malrotation of intestine	155	0.2
Duodenal atresia	152	0.2
Congenital omphalocele	142	0.2
Imperforate anus	123	0.1
Oesophageal atresia	123	0.1
Nephroblastoma	113	0.1

Sepsis	Incidence	% of total
Sepsis	1497	1.8
Meningococcal septicaemia	1031	1.2
Septic shock	296	0.4
Septicaemia	170	0.20
Meningococcal meningitis with meningococcal septicaemia	37	0.04
Sepsis syndrome	34	0.04
Gp A streptococcal septicaemia	26	0.03
Meningococcal infection	22	0.03
Necrotising fasciitis	22	0.03
Bacterial endocarditis	14	0.02

Chapter 6

MORTALITY RATES AT ALDER HEY CHILDREN'S HOSPITAL VERSUS THE OVERALL UK PICU RATE AS REPORTED TO THE PAEDAITRIC INTENSIVE CARE NETWORK.

The Royal Liverpool Children's Hospital has been using SDD on their PICU since 1992. The mortality rate reported in 2005 by Sarginson was relatively low at 5%. One might expect the use of SDD to affect the mortality rates reported to PICANet for Alder Hey compared to the UK average.

Methods

Using the PICANet database the mortality rate for 5 years from 2004-2008 was analysed to see if there were any differences in mortality rates between Alder Hey and the rest of the UK. Simple statistical analyses were used, including comparison of averages and ANOVAs.

The Paediatric Index of Mortality was designed to provide a predicted mortality for a patient by following a well-defined algorithm. Predicted mortalities are good when dealing with several patients, because the average predicted mortality for a group of patients is an indicator for the morbidity of these patients (Slater A). So PIM is a scoring system for rating the severity of medical illness for children. PIM2 was subsequently described as a refinement on PIM and provides a good way to benchmark different sets of patients.

The standardised mortality ratio (SMR) is the ratio of observed deaths to expected deaths, where expected deaths are calculated from PIM or PIM2 for a typical sub-set with the same age and gender mix by looking at the death rates for different ages and genders in the larger population. The SMR may be quoted as either a ratio or a percentage. If the SMR is quoted as a ratio and is equal to 1.0, then this means the

number of observed deaths equals that of expected cases. If higher than 1.0, then there is a higher number of deaths than is expected.

Results

83,863 children were admitted during the 5-year period between 2004 and 2008 throughout the UK with an overall mortality rate of 4.85 % (Table 6.1). The severity of illness as measured by the PIM score was 0.0579. At Alder Hey 5369 children were admitted during this period with a mortality of 5.34% and a PIM score of 0.0532. The standardised mortality rate (SMR) derived from PIM for the UK was 0.8376 and for Alder Hey 1.0049. A more detailed look into the annual rates revealed a similar trend. From 2006 onwards PIM2 was introduced and reported. As described above SMR is calculated by dividing the expected mortality rate by the observed mortality rate. The expected rate is derived from the PIM and PIM2 scores.

As would be expected those children who survive in AH had on average a statistically significant lower PIM score 0.0463 compared to those who do not survive 0.170 ($p=0.009$) and SMR of 1.165 vs. 0.33 ($p=0.008$) (Table 6.2). The PIM2 score for those children who survive was 0.042 vs. 0.217 for those who died. The SMR for the former was 1.156 vs. 0.225 or a 75% risk of mortality. A similar pattern is seen nationally (Table 6.2).

In those children with a risk of mortality of 5% or less, the point has already been made that no therapy is likely to reduce the mortality rate significantly. To explore the possibility that SDD is more effective in the higher risk groups the overall data was stratified into different PIM groups (Table 6.3). Ranges used were <0.05; 0.05-1.0; 1.0-1.5; 1.5-2.0; 2.0-3.0; 3.0-4.0; >4.0.

There was no significant difference between the UK population and the AH subset in all but the 3-4.0 PIM risk group ($p=0.04$, $n=191$ vs. 12) (Table 6.4). Again the number of patients in each group are relatively small for the AH subset and to detect a difference a larger sample size would be needed.

Conclusions

The simplest conclusion that can be drawn from the data is that SDD does not have a significant impact on reducing mortality in critically ill children. However, this may be too simplistic. Other factors have to be taken into consideration. Sample size in particular. With the overall PICANet dataset it was not possible to extract any information on morbidity or infection rates, so other reported beneficial aspects of SDD could not be considered.

Although the number of children admitted to AH was 5369 the death rate was still on average 5.34%. The mortality rate for the PIM > 4 group was 0.735 or a 73.5% risk of death. However the numbers in this group was only n=34.

Similarly the only statistically significant difference observed was in the PIM 3-4 group which had the lowest number of patients and statistical testing is really not very useful.

Table 6.1 Survival rate for the five year period 2004-2008 and overall PIM and SMR.

Liverpool										
	Admissions	Alive	Dead	% Mort	PIM Overall Avg	S.D.	SMR	PIM2 Overall Avg	PIM2 Overall SD	SMR 2
2004	992	940	52	5.2	0.0479	0.073	1.09	----	----	
2005	1034	962	72	7.0	0.0519	0.079	1.35	----	----	
2006	1117	1071	46	4.0	0.0536	0.084	0.75	0.051	0.099	0.792
2007	1084	1019	65	6.0	0.0554	0.086	1.08	0.052	0.103	1.161
2008	1142	1090	52	4.6	0.0568	0.090	0.81	0.050	0.095	0.916
Total	5369	5082	287	5.34	0.0532	0.083	1.00	0.051	0.099	1.052

National										
	Admissions	Alive	Dead	% Mort	PIM Overall Avg	S.D.	SMR	PIM2 Overall Avg	PIM2 Overall SD	SMR 2
2004	14413	13654	759	5.3	0.0558	0.092	0.94	----	----	----
2005	14767	14050	717	4.9	0.0563	0.093	0.86	----	----	----
2006	15366	14553	813	5.3	0.0577	0.097	1.10	0.113	0.058	0.467
2007	17647	16796	851	4.8	0.0589	0.094	0.93	0.109	0.058	0.441
2008	21670	20722	948	4.4	0.0579	0.091	0.76	0.109	0.057	0.402
Total	83863	79796	4067	4.85	0.0579	0.093	0.84	0.058	0.109	

Table 6.2 PIM and SMR for those who survive and those who die.

Liverpool												
	PIM Alive Avg	S.D.	SMR	PIM dead Avg	S.D.	SMR	PIM2 Alive Avg	S.D.	SMR	PIM2 Dead	S.D.	SMR
2004	0.0437	0.0637	1.19	0.1236	0.1478	0.421	----	----	----	----	----	----
2005	0.0442	0.0519	1.58	0.1551	0.2059	0.451	----	----	----	----	----	----
2006	0.0467	0.0574	0.86	0.2116	0.2648	0.189	0.0429	0.0729	0.932	0.2266	0.2928	0.229
2007	0.0472	0.0617	1.27	0.1837	0.2156	0.327	0.0409	0.0705	1.467	0.2222	0.2657	0.315
2008	0.0498	0.0611	0.92	0.1740	0.280	0.264	0.0430	0.0676	1.070	0.2014	0.2852	0.199
Average	0.0463		1.165	0.1696		0.33	0.042		1.156	0.217		0.225
p				0.009		0.008				0.002		0.02

National												
	PIM Alive Avg	S.D.	SMR	PIM dead Avg	S.D.	SMR	PIM2 Alive Avg	S.D.	SMR	PIM2 Dead	S.D.	SMR
2004	0.04828	0.06764	1.09	0.19829	0.24556	0.27	----	----		----	----	
2005	0.04836	0.0664	1.00	0.21342	0.25680	0.23	----	----		----	----	
2006	0.04874	0.06767	1.09	0.21820	0.26022	0.24	0.08383	0.04750	0.63	0.27941	0.25160	0.19
2007	0.05173	0.0721	0.93	0.20065	0.24449	0.24	0.08591	0.04893	0.56	0.26361	0.23563	0.18
2008	0.0529	0.06758	0.83	0.21421	0.00425	0.20	0.0812	0.04863	0.54	0.27592	0.24287	0.16
Average			0.99			0.24			0.58			0.18
p				0.000003		0.00005				.00009		.0027

AH vs. N			0.260			0.113			0.081			0.260

Table 6.3a PIM and SMR for Alder Hey and nationally (6.3b) at various levels of PIM. Overall mean SMRs highlighted in red.

Liverpool														
	Total Deaths	No. Death PIM<0.05	%Mort for PIM <0.05	Avg. PIM<0.05	SMR	No. Death PIM 0.05-1.0	%Mort PIM 0.05-1.0	Avg. PIM 0.05-1.0	SMR	No. Death PIM 1.0-1.5	%Mort PIM 1.0-1.5	Avg. PIM 1.0-1.5	SMR
2004	52	16	2.3	0.027	0.9	13	6.6	0.069	1.0	13	21.0	0.116	1.8
2005	72	16	2.3	0.027	0.8	29	14.4	0.072	2.0	12	17.9	0.129	1.4
2006	46	17	2.2	0.030	0.7	8	4.3	0.071	0.6	4	5.9	0.128	0.5
2007	65	16	2.2	0.033	0.7	15	7.1	0.068	1.0	8	12.3	0.114	1.1
2008	52	18	2.4	0.029	0.8	10	4.1	0.064	0.6	11	13.9	0.131	1.1
Total	287	83	2.3	0.029	0.8	75	7.2	0.069	1.0	48	14.1	0.123	1.1

No. Death PIM 1.5-2.0	%Mort for PIM 1.5-2.0	PIM 1.5-2.0	SMR	No. Death PIM 2.0-3.0	%Mort for PIM 2.0-3.0	PIM 2.0-3.0	SMR	No. Death PIM 3.0-4.0	%Mort for PIM 3.0-4.0	PIM 3.0-4.0	SMR	No. Death PIM >4.0	%Mort for PIM >4.0	PIM >4.0	SMR
1	6.3	0.15	0.4	5	45.5	0.237	1.9	1	33.3	0.338	0.986	3	37.5	0.693	0.5
2	8.3	0.189	0.4	3	17.6	0.241	0.7	3	50.0	0.328	1.524	7	77.8	0.718	1.1
4	13.3	0.175	0.8	2	10.0	0.242	0.4	2	33.3	0.315	1.058	9	60.0	0.703	0.9
8	22.9	0.174	1.3	8	28.6	0.239	1.2	4	57.1	0.372	1.536	6	66.7	0.784	0.9
1	2.9	0.172	0.2	1	4.2	0.288	0.1	2	33.3	0.335	0.995	9	69.2	0.77	0.9
16	11.5	0.174	0.7	19	19.0	0.242	0.8	12	42.9	0.342	1.253	34	63.0	0.735	0.9

Table 6.3b PIM and SMR for National data at various levels of PIM. Mean SMRs are highlighted in red for ease of comparison.

National														
	Total Deaths	No. Death PIM<.05	%Mort for PIM <0.5	Avg. PIM <.05	SMR	No. Death PIM.05-1.0	%Mort PIM 0.5-1.0	PIM 05-1.0	SMR	No. Death PIM1.0-1.5	%Mort PIM 1.0-1.5	PIM 1.0-1.5	SMR
2004	759	214	2.193	0.028	0.77	173	9.94	0.073	1.36	82	8.98	0.122	0.74
2005	717	195	1.955	0.028	0.69	147	8.11	0.073	1.11	100	10.6	0.122	0.87
2006	813	229	2.197	0.028	0.78	163	8.66	0.072	1.21	107	11.4	0.125	0.91
2007	851	236	2.027	0.027	0.76	186	7.89	0.074	1.06	115	9.5	0.124	0.76
2008	948	265	1.918	0.028	0.68	179	5.94	0.073	0.81	113	7.0	0.126	0.56
Total	4067	1139	2.048	0.028	0.73	848	7.85	0.073	1.07	517	9.2	0.124	0.74

No. Death PIM 1.5-2.0	%Mort for PIM 1.5-2.0	PIM 1.5-2.0	SMR	No. Death PIM 2.0-3.0	%Mort for PIM 2.0-3.0	PIM 2.0-3.0	SMR	No. Death PIM 3.0-4.0	%Mort for PIM 3.0-4.0	PIM 3.0-4.0	SMR	No. Death PIM >4.0	%Mort for PIM >4	PIM >4	SMR
43	11.56	0.171	0.676	71	23.8	0.235	1.01	36	30.8	0.345	0.91	108	57.8	0.733	0.788
61	14.77	0.172	0.859	59	19.3	0.243	0.80	25	24.3	0.335	0.73	126	63.0	0.718	0.877
64	15.35	0.175	0.877	60	18.4	0.237	0.78	37	27.0	0.343	0.79	152	62.3	0.709	0.879
66	13.23	0.173	0.765	81	19.9	0.242	0.82	46	25.8	0.353	0.73	120	50.4	0.741	0.680
70	11.33	0.171	0.662	111	20.6	0.238	0.86	47	23.4	0.342	0.68	142	57.0	0.77	0.741
304	13.11	0.172	0.762	382	20.4	0.239	0.85	191	26.0	0.343	0.76	648	58.0	0.734	0.790

Table 6.4 Mortality rates and SMRs for various PIM ranges with significance levels. There was no significant difference between the UK population and the AH subset in all but the 3-4.0 PIM risk group (p=0.04, n=191 vs. 12).

Mortality Rates	PIM <0.5	PIM 0.5-1	PIM 1.0-1.5	PIM 1.5-2	PIM 2.0-3.0	PIM 3.0-4.0	PIM >4.0
Liverpool	2.3	7.2	14.1	11.5	19.0	42.9	63.0
GOSH	2.8	8.6	11.4	17.6	23.9	31.8	59.2
National	2.0	7.9	9.2	13.1	20.4	26.0	58.0
p	0.09	0.68	0.18	0.48	0.91	0.05	0.58

SMRs	PIM <0.5	PIM 0.5-1	PIM 1.0-1.5	PIM 1.5-2	PIM 2-3.0	PIM 3.0-4.0	PIM >4.0
Liverpool	0.78	1.04	1.14	0.66	0.79	1.25	0.90
GOSH	1.00	1.18	0.76	1.02	0.99	0.92	0.84
National	0.73	1.07	0.74	0.76	0.85	0.76	0.79
p	0.45	0.82	0.19	0.47	0.93	0.04	0.57

Chapter 7

CONCLUSIONS

Can SDD reduce infection morbidity in paediatric intensive care?

The major difference between paediatric and adult intensive care is the mortality rate. Adults have in the past had a mortality rate approaching 30%. In the early days of adult ICU the rate for sepsis was as high as 80%. More recently, the overall rate has decreased to around 20%. This is still much higher than for paediatrics. The overall mortality rate as reported to PICANet is around 5.0% nationwide when adjusted for severity of illness the risk of mortality is very low compared to adults.

The causes for death also are different from those in adults. There are a larger proportion of deaths as a result of withdrawal of therapy as a consequence of incurable background pathology (Sands R). A recent retrospective study reported the characteristics of death in a single PICU over a 10 year period (Sands R). The morality rate was 5.1% and comprised of 204 children. The authors found that the most common cause of death in that particular tertiary unit was managed withdrawal of life-sustaining medical therapy. This mode of death was attributed to 54.9% of all deaths over the 10 year period.

The data presented by Sands and colleagues is useful in that it is the result of a single centre in which patient notes can by checked for accuracy of diagnosis of death. The numbers were sufficiently small enough to allow this validation. Only 204 case notes would have to have been reviewed. However, it is not clear whether this single center study reflects the pattern of death throughout the country.

The causes of death are described in the UK for children admitted to PICU to be able to compare them with those in adults. There are very few reports describing the causes of death of children on PICU. The difficulty of obtaining the cause of death is that it is often influenced by decisions to withdraw treatment in a number of non-

viable cardiac or metabolic conditions. Also the reliability of the description of the cause of death can be questioned. Admission data however is collected according to recognised coding systems and it could be argued is more useful in giving an idea of the distribution of diseases within organ systems, particularly in the paediatric world since the introduction of the PICANet database.

Consequently, the impact of SDD on the all cause mortality is limited as the illness profile for children and adults is different. If mortality does not result from a pneumonic or septic process in equal proportion to adult the SDD is unlikely to produce a similar reduction in either as seen in the adult ICU world.

However, other measures of effectiveness and reduction of morbidity may confirm SDD's usefulness. Recently, the use of antibiotics on neonates have been shown to result in multiresistant Enterobacteriaceae strains which were found at high frequency in the infants during their stay in the NICU and persisted in a proportion of infants (Millar LM). By reducing the amount of parenteral antibiotics used SDD may have an impact on this increasing incidence of resistance.

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Appendix

Publications as First Author

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Selective decontamination of the digestive tract in critically ill children: Systematic review and meta-analysis

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Objective: We examined the impact of selective decontamination of the digestive tract on morbidity and mortality in critically ill children.

Data Sources: We searched MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and previous meta-analyses.

Study Selection: We included all randomized controlled trials comparing administration of enteral antimicrobials in selective decontamination of the digestive tract with or without a parenteral component with placebo or standard therapy used in the controls.

Data Extraction: The primary end point was the number of acquired pneumonias. Secondary end points were number of infections and overall mortality. Odds ratios were pooled with the random effect model.

Data Synthesis: Four randomized controlled trials including 335 patients were identified. Pneumonia was diagnosed in five of 170 patients (2.9%) for selective decontamination of the digestive tract and 16 of 165 patients (9.7%) for controls (odds ratio [OR], 0.31; 95% confidence interval [CI], 0.11–0.87; $p = .027$). Overall mortality for selective decontamination of the digestive tract was 13 of 170 (7.6%) vs. control, 11 of 165 (6.7%) (OR, 1.18; 95% CI, 0.50–2.76; $p = .70$). In three studies (n = 109), infection occurred in ten of 54 (18.5%) patients on selective decontamination of the digestive tract and 24 of 55 (43.6%) in the controls (OR, 0.34; 95% CI, 0.05–2.18; $p = .25$).

Conclusions: In the four available pediatric randomized controlled trials, selective decontamination of the digestive tract significantly reduced the number of children who developed pneumonia. (Pediatr Crit Care Med 2012; 13:000–000)

Key Words: critically ill children; infection; mortality; pediatric; pneumonia; randomized controlled trial (RCT); selective decontamination of the digestive tract (SDD)

Since the recent randomized controlled trial (RCT) on selective decontamination of the digestive tract (SDD) demonstrated a significant reduction in mortality in critically ill adults in intensive care (1), there has been a resurgence of interest in the value of SDD.

Nosocomial infection is associated with changes in the gut flora and critical illness profoundly changes body flora, both qualitatively and quantitatively (2), and promotes a shift from 1) normal (3) to abnormal carriage (4, 5) and 2) low- to high-grade carriage or gut overgrowth (6).

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There are now 65 RCTs and 11 meta-analyses demonstrating a significant reduction in nosocomial pneumonia morbidity and more importantly mortality in adult ventilated patients in intensive care.

We reviewed all RCTs performed in children to determine whether SDD is also effective in children. The use of SDD in pediatrics has been very limited in contrast to the adult experience. This is in part the result of the low rates of infection and mortality in the general pediatric population. The overall mortality rate in pediatric intensive care varies between 5% and 10% (7). Total inhouse mortality (3.74%) can differ a little from outside admissions mortality (3.94%) (8). Crude mortality rates from the Australian and New Zealand 2009 census reported a rate of 2.9% (9). These are low rates compared with the 20% to 30% in adults. There are of course subgroups of children who are at greater risk of infections and also death that might benefit from the use of SDD.

The participants in this systematic review and meta-analysis include children up to the age of 16 yrs who received selective decontamination of the digestive tract. The reason for undertaking the meta-analysis was to assess the four pediatric trials with respect to the primary end point of pneumonia, the secondary end point of overall infection, and finally overall mortality from the available RCTs.

Data Sources

Search Strategy. RCTs were obtained by searching electronic databases EMBASE and MEDLINE with no restriction on language or gender. Search key words were SDD, selective decontamination of the digestive tract, selective bowel decontamination, and gut decontamination. In addition, the authors searched their personal archives and published meta-analyses on SDD.

Inclusion and Exclusion Criteria. We established inclusion and exclusion criteria before reviewing abstracts and articles. We included all RCTs comparing enteral administration of the SDD antibiotics (oropharyngeal, intestinal, or both) with or without a parenteral component with no treatment or placebo in the controls. RCTs with usable information by outcome were finally included in the meta-analysis. Studies were excluded for the following reasons: 1) nonrandomized studies or studies with an inappropriate

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design; 2) double publications or studies including data extracted from main publication; 3) both study arms received SDD; and 4) studies including neutropenic, stem cell, and bone marrow transplant patients.

Data Extraction of Outcome Measures

Three investigators (AP, LS, HvS) independently retrieved the published findings from each study and compared the sets of data. Any disagreement was resolved by discussion. The following data were sought for each study and recorded on standard collection sheets: specific antimicrobials used and routes; number of patients in each arm; number of patients with pneumonia and infection; and number of deaths.

Quality Assessment

The quality of each study was assessed with reference to a predefined list of seven criteria in a scoring system of 0–14 reported originally by Heyland et al (10) and modified by Brazzi et al (11) and Silvestri et al (12). The criteria used here included randomization, study blinding, patient selection, population description, reproducibility, definitions of infection, and carriage (12). The assessment was made by three investigators, (AP, LS, HvS).

Definitions

Pneumonia was defined based on the individual clinical and laboratory criteria used by the authors of the selected RCTs, i.e., fever, increased volume and purulence of lower airway secretions, a culture positive for potential pathogens in high concentrations ($\geq 10^5$ quantitatively or $\geq 2+$ semiquantitatively), and the presence of a new or evolving pulmonary infiltrate on the chest radiograph (13).

All other infections were defined according to Centers for Disease Control and Prevention criteria (13).

Statistical Analysis

The primary end point was the number of children developing pneumonia during treatment with SDD. Secondary end points were overall infection and mortality. We planned *a priori* the following subgroup analysis of the three end points: 1) type of regimen used (parenteral plus enteral or enteral only); 2) randomization procedures (adequate or inadequate); and 3) blinding of patients and caregivers to allocated treatment (blinded or unblinded). We hypothesized that the treatment effect would be lower with enteral only regimen, in adequate randomization, and in blinded studies. Randomization was adequate when patients were randomized by telephone or a central office. A study was blinded when both caregivers and outcome assessors were blinded.

Checking for heterogeneity across studies and random-effects meta-analysis were undertaken (14). Results are presented as odds ratio (ORs) with 95% confidence intervals (CIs) using the random effects model. The Cochran Q statistic for heterogeneity was used both for the outcome measures and through subgroup analyses; we considered heterogeneity to be significant if the p value was $<.10$. I^2 was also evaluated using the formula $100\% \times (Q-df)/Q$ where Q is Cochran Q and df the degree of freedom (number of studies−1). Negative values of I^2 are equal to 0%. I^2 <30% indicates mild heterogeneity and 30% to 50% moderate and >50% severe heterogeneity. Computations were performed using EasyMA software (15).

Data Synthesis

Search Findings and Characteristics of the Studies. The preliminary search identified 153 potentially relevant studies (Fig. 1). Of these studies, 88 were excluded: 64 studies were not randomized, 21 RCTs were double publications, and three RCTs used SDD in both arms. We identified 65 potentially appropriate RCTs of whom 61 were excluded because they were not performed in children. A final sample of only four RCTs, which enrolled a total of 335 patients (170 SDD, 165 controls), was the basis for the systematic review and meta-analysis. One of the four studies was in burn patients only and two of the others were also special populations, cardiac, and liver transplant. However, these are the only four from which some impression of efficacy may be gained (Table 1).

Leclerc and Noizet (16) undertook a systematic review of the four pediatric studies in 2004 but did not undertake a meta analysis of the data they described. We go further and describe the four RCTs (17–20) in terms of quality on a previously devised score. The trials include a varied population ranging from severely burned pediatric patients, to children in pediatric intensive care units, to children undergoing liver transplantation. Quality assessment for all trials using the methods described by Heyland (9), Brazzi (10), and Silvestri (11) resulted in a median

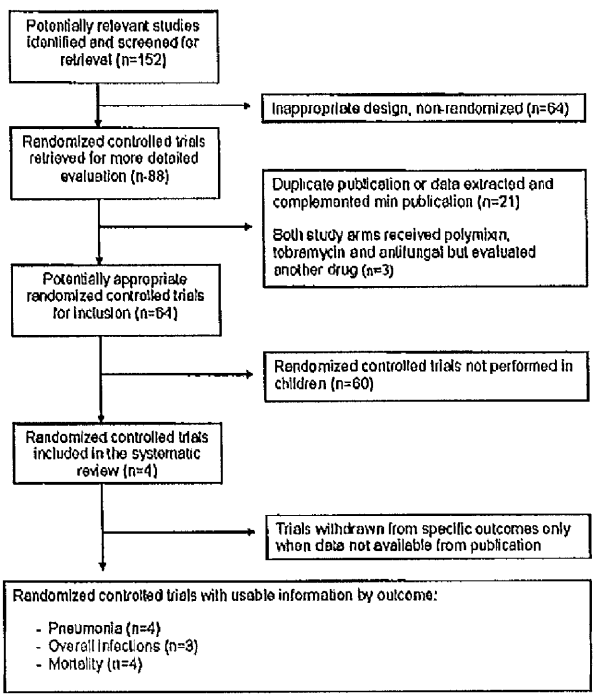

Figure 1. Selection procedure for studies meeting the inclusion criteria.

Table 1. General characteristics of randomized controlled trials of selective decontamination undertaken in children

Author (Reference)	Year	Country	No.	Blinding	Randomization	First End Point	Outcome Selective Decontamination of the Digestive Tract vs. Control	Population	Regimen Enteral	Regimen Parenteral	Aerobic Gram-Negative Bacilli	Yeasts	Site
Zobel et al (17)	1991	Austria	50	No	Adequate	Colonization Infection rates	0% vs. 52% 8% vs. 36%	Cardiac surgery	Cefotaxime		P, T	A	O, I
Smith et al (18)	1993	United States	36	No	Adequate	Infection rates Length of stay Mortality	11% vs. 50% 7 days vs. 8 days 14% vs. 23%	Liver transplants	Cefotaxime/ ampicillin 2 arms		P, T	A	O, I
Ruza et al (19)	1998	Spain	226	No	Inadequate	Infection rates Length of stay Mortality	39% vs. 38% 10.4 days vs. 9.6 days 4.5% vs. 5.2%	Invasive instrumentation on intensive care unit	None		Col, T	Ny	–, I
Barret et al (20)	2001	United States	23	Yes	Inadequate	Infection rates Mortality	25 vs. 45% 8% vs. 18%	Severe burns	Vancomycin, amikacin, piperacillin		P, T	A	–, I

P, polymyxin; T, tobramycin; Col, colistin; A, amphotericin; Ny, nystatin; O, oropharynx; I, intestine.

score of 9.2 (range, 8.4–9.9). This compares well with previous quality assessment of all the SDD meta-analyses of adult and pediatric data, which resulted in a median score of 9.0 (interquartile range, 8–11) (11). Zobel et al (17) received a score of 10.3, Smith et al 9.7 (18), Ruza et al (19) 7.3, and Barret et al (20) achieved a score of 8.7.

Zobel and colleagues (17) studied 50 children in a cardiac pediatric intensive care unit. All patients were endotracheally intubated and mechanically ventilated. SDD was given to 25 children in a prospective RCT after cardiac surgery in addition to the routine antibiotic regimen and 25 children were controls. During the study, colonization with Gram-negative microorganisms and yeasts in the oropharynx and digestive and respiratory tracts increased up to 52% in the control group. There was no colonization with these micro-organisms in the treatment group. The rates of acquired secondary infections in the control and treatment groups were 36% and 8%, respectively ($p < .025$). There were no differences in length of intensive care or mortality. The authors concluded that SDD produced a significant reduction of the colonization rate with Gram-negative bacteria and yeasts in critically ill pediatric patients after cardiac surgery and needing intensive care for >3 days. SDD also significantly reduces the Gram-negative infection rate of the respiratory system. However, it did not alter intensive care unit length of stay or mortality rate.

Smith and colleagues (18) undertook the first prospective RCT of short-term SDD in children having orthotopic liver transplantation. Although not specifically documenting that all the children were ventilated, because the patients were liver transplants admitted to the intensive care unit postoperatively, it was assumed both groups were ventilated. Oral and nasogastric SDD, in addition to routine parenteral antibiotics, was given to 18 children having transplants and only routine parenteral antibiotics to the control group of 18. There was no difference in the group's demographics, intensive care, or hospital length of stay. During the study, 14 Gram-negative infections (intra-abdominal abscess, seven; septicemia, five; pneumonia, one; urinary tract, one) developed in the 36 patients studied. Mortality was not significantly different in the two groups. There were significantly fewer patients with Gram-negative infections in the SDD group: three of 18 patients (11%) vs. 11 of 18 patients (50%) in the control group ($p < .001$). There was also significant reduction in aerobic Gram-negative flora in the stool and pharynx. The authors concluded that short-term postoperative SDD significantly reduces Gram-negative infections in children having orthotopic liver transplantation.

In a prospective, randomized, nonblinded and controlled trial, Ruza et al (18) studied children aged 1 month to 14 yrs who had any manipulation or instrumentation such as mechanical ventilation, vascular cannulation, monitoring of intracranial pressure, thoracic or abdominal drainage, bladder catheterization, peritoneal dialysis, and/or presented a neurologic coma during a >3-day stay in a tertiary pediatric intensive care unit (19). Over a 2-yr period, 226 children were included in the study, the treatment group comprised 116 patients and the control group 110 patients. A total of 164 (73%) children were ventilated, 91 (55.5%) receiving SDD and 73 (44.5%) in the control group ($p < .05$). The treatment group was given colimycin, tobramycin, and nystatin administered orally or through a nasogastric tube, whereas no oropharyngeal decontamination was implemented. Using univariate analysis, SDD did not significantly reduce the incidence of nosocomial infection, the length of stay, or mortality. However, using multivariate analysis, SDD decreased the incidence of respiratory and urinary tract infections, reducing the risk of such infections to one of five and one of three, respectively. Ruza and colleagues (19) concluded that SDD was effective in controlling respiratory and urinary tract infections in children admitted to the pediatric intensive care unit, but it did not reduce the incidence of other types of nosocomial infection.

Finally, Barret et al (20) studied 23 children with severe burns (Table 1). After randomization, SDD was given in a double-blind manner to 11 children and 12 received placebo. The control group received mechanical ventilation for 8 ± 2 days and the SDD group for 14 ± 5 days with no significant difference. Both groups received parenteral antibiotics; the SDD group also received oral and nasogastric enteral antibiotics including polymyxin E, tobramycin, and amphotericin B. Demographics, hospital course, microbiology results, complications, infectious episodes, and serum levels of interleukin-1β, interleukin-6, interleukin-10, and tumor necrosis factor-α were

compared. There was a similar incidence of colonization rates to the wound, sputum, nasogastric aspirates, and feces. The incidence of pneumonia, sepsis, and other complications was also similar in both groups as were serum levels of all cytokines studied. The authors noted a significantly higher incidence of diarrhea ($p = .003$) in the children who received SDD. They concluded that SDD is not effective in decreasing bacterial colonization and infectious episodes in severely burned pediatric patients.

Pneumonia

All four RCTs included 335 patients in total (Fig. 2). Pneumonia occurred in five of 170 patients (2.9%) of those who received SDD and in 16 of 165 patients (9.7%) in the control group. This was a significant reduction in the incidence of pneumonia with SDD (OR, 0.31; 95% CI, 0.11–0.87; $p = .027$). Heterogeneity was not observed (chi square = 2.51, $p = .47$, $I^2 = 0$) (Tables 2 and 3).

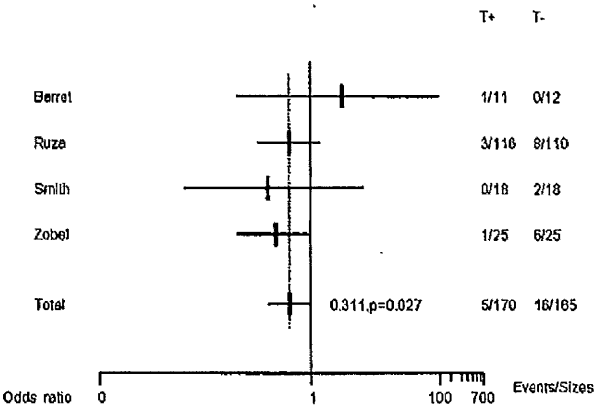

Figure 2. Effect of selective decontamination of the digestive tract on pneumonia.

Table 2. Data extracted from four randomized controlled trials of selective digestive decontamination in pediatric population

	Patients		Patients With Infection		Patients With Pneumonia		Mortality	
Author	SDD	C	SDD	C	SDD	C	SDD	C
Zobel	25	25	2	10	1	6	3	2
Smith	18	18	3	11[a]	0	2	2	3
Ruza	116	110	NA	NA	3	8	6	5
Barret	11	12	5	3	1	0	2	1

SDD, selective digestive decontamination; C, control; NA, not available.
[a]Patients with Gram-negative infections.

Infection

In three RCTs, including 109 children, infections of various origins were confirmed in ten of 54 (18.5%) children on SDD and in 24 of 55 (43.6%) children in the control group. SDD had no impact on general infection rates with no overall difference between the groups (OR, 0.34; 95% CI, 0.05–2.18; $p = .25$) (Tables 2 and 3).

Mortality

The impact of SDD on mortality was analyzed in all four studies. Overall mortality for those who received SDD vs. those who did not was 13 of 170 (7.6%) and 11 of 165 (6.7%), respectively, demonstrating no reduction in the odds of death (OR, 1.18; 95% CI, 0.50–2.76; $p = .70$) (Tables 2 and 3).

Subgroup Analysis

Subgroup analyses of type of SDD regimen, randomization, and blinding are shown in Table 4. A significant impact on infections and pneumonia was found with the use of the full protocol of parenteral and enteral antimicrobials rather than solely enteral antimicrobials. A significant impact on pneumonia and overall infection was demonstrated when randomization was adequate and in unblinded studies. The subgroup analyses for mortality were consistent with previous pooled results whether the intervention was parenteral/enteral or enteral, whether the design was blinded or not, and whether the randomization process was adequate or not. The Q and I^2 tests for heterogeneity yielded nonsignificant results in all comparisons.

DISCUSSION

There are very few pediatric studies on the use of SDD in critically ill children. Although there has been a systematic review of the four studies (16), this is the first meta-analysis of these currently available RCTs. The numbers of children included are relatively small, which probably accounts for the lack of significant effect on mortality or overall infection. However, even with relatively few numbers, there is still a significant reduction in pneumonia rates. Using a recognized assessment tool for quality of studies included in meta-analyses, the four studies resulted in a very acceptable median value for quality of the studies.

The new finding of this meta-analysis in pediatrics is that SDD does not significantly reduce overall infections nor mortality. However, there is a significant impact of SDD on reduction of the incidence of pneumonia in critically ill children (OR, 0.34; $p = .027$). Previous reports have demonstrated that the infection rate in children using SDD is very low over a 4-yr period (21).

Furthermore, on subgroup analysis, when the full SDD protocol of enteral plus parenteral antibiotics is used, there is significant reduction in overall infections (OR, 0.13 [0.04–0.40]; $p < .001$). However, this subgroup analysis has to be taken with considerable caution because it involves small numbers of patients. The enteral component of SDD when used alone does not have an impact.

Because invasive mechanical ventilation is a major risk factor for nosocomial pneumonia, it is important to note that in the Zobel et al (17), Smith et al (18), and Barret et al (20) studies, all patients were ventilated and in the Ruza et al (19) study, 73% of the study was ventilated equally distributed. All four pediatric RCTs used noninvasive techniques to diagnose pneumonia consisting of tracheal aspirate and/or sputum. Invasive diagnosis of pneumonia with a protected specimen brush or bronchoalveolar lavage after bronchoscopy is associ-

Table 3. Meta-analysis of the impact of selective digestive decontamination on secondary end points

Outcome	Randomized Controlled Trials	No. of Patients		No. of Patients With Outcome		Odds Ratio (95% Confidence Interval)	p	I^2
		Selective Digestive Decontamination	Control	Selective Digestive Decontamination	Control			
Pneumonia	4	170	165	5	16	0.31 (0.11–0.87)	.027	0%
Infection	3	54	55	10	24	0.34 (0.05–2.18)	.25	4.7%
Mortality	4	170	165	13	11	1.18 (0.50–2.76)	.70	0%

Odds ratio less than the unit favors treatment; odds ratio above the unit favors controls.

Table 4. Subgroup analysis of the impact of selective digestive decontamination on the end points of pneumonia, infection, and mortality

End Points	No. of Randomized Controlled Trials	No. of Patients		No. of Events		Odds Ratio (95% Confidence Interval)	p
		Selective Digestive Decontamination	Control	Selective Digestive Decontamination	Control		
Pneumonia							
Parenteral plus enteral	2	43	43	1	8	0.14 (0.02–0.89)	.037
Enteral only	2	127	122	4	8	0.65 (0.07–6.34)	.71
Randomization adequate	2	43	43	1	8	0.14 (0.02–0.89)	.037
Randomization inadequate	2	127	122	4	8	0.65 (0.07–6.34)	.71
Blinded	1	11	12	1	0	5.97 (0.07–471.43)	NE
Not blinded	3	159	153	4	16	0.26 (0.09–0.76)	.013
Infections							
Parenteral plus enteral	2	43	43	5	21	0.13 (0.04–0.40)	<.001
Enteral only	1	11	12	5	3	2.50 (0.43–14.61)	NE
Randomization adequate	2	43	43	5	21	0.13 (0.04–0.40)	<.001
Randomization inadequate	1	11	12	5	3	2.50 (0.43–14.61)	NE
Blinded	1	11	12	5	3	2.50 (0.43–14.61)	NE
Not blinded	2	43	43	5	21	0.13 (0.04–0.40)	<.001
Mortality							
Parenteral plus enteral	2	43	43	5	5	1 (0.26–3.84)	1
Enteral only	2	127	122	8	6	1.32 (0.44–3.95)	.62
Randomization adequate	2	43	43	5	5	1 (0.26–3.84)	1
Randomization inadequate	2	127	122	8	6	1.32 (0.44–3.95)	.62
Blinded	1	11	12	2	1	2.44 (0.19–31–54)	NE
Not blinded	3	159	153	11	10	1.08 (0.44–2.66)	.87

NE, not evaluated as only one study was included.
The Q and I^2 tests for heterogeneity were not significant in all comparisons. Odds ratio <1 favors treatment; odds ratio >1 favors controls.

ated with halving the diagnosis of pneumonia (22). However, invasive management does not impact on mortality (23). So using noninvasive techniques in pediatric is a good surrogate measure of diagnosing pneumonia.

We raised the question 15 yrs ago whether mortality or morbidity was the goal to measure quality outcomes against (24). Debate has ensued and morbidity is certainly now recognized as a valuable end point, particularly when it improves quality of care for the patient. Given this acknowledgment, the question has to be asked whether withholding SDD from critically ill children is now justifiable given the extensive adult literature (25) and now the beginnings of a pediatric evidence base, albeit limited? A recent French Consensus Conference recommended SDD as pneumonia prophylaxis in critically ill children (26). Unfortunately, this recommendation has not been implemented. There is still antipathy to SDD from various sectors. Microbiologists and some intensivists dislike the use of such broad-spectrum oral antibiotics and continue to have concerns over emerging resistance. Perhaps more importantly, SDD uses readily available antibiotics and consequently has never been marketed commercially by a large pharmaceutical company and so has not benefited from the persuasive professional marketing techniques available to these agencies. However, if there is a technique or treatment that convincingly demonstrates a reduction in morbidity, should we not use it?

In terms of costs of implementing SDD, a study by Garcia-San Vicente (27) compared two periods of 1 yr: before and after using SDD in the adult intensive care unit. Surveillance cultures did not significantly increase the workload nor the cost of processing the samples. The explanation provided by the authors was that the increase in surveillance samples was offset by the decrease in diagnostic samples such as blood samples, bronchioalveolar lavage, and urine. During the SDD period, they reported an increase in *Pseudomonas aeruginosa* resistance to imipenem, tobramycin, and ciprofloxacin. However, the changes in resistance do not refer to the two periods of study. The author described changes in resistance between 1996 and 2007. The studied periods were 2001–2002 pre-SDD and 2002–2003 post-SDD (28). The authors recognized that their conclusion about *P. aeruginosa* resistance was not well supported (29).

Also the costs during SDD may have been overestimated because surveillance of tracheal and gastric aspirate is not necessary. Costs adjusted for length of stay also confirm that surveillance during SDD is

not associated with increased expenditure (26). Although the cost-effectiveness of SDD has not yet been formally calculated, the daily cost of using SDD was estimated at approximately 12 Euros (1).

A study by Oostdijk and colleagues (30) report the emergence of multidrug-resistant bacterial organisms. They conclude that SDD and also selective oral decontamination have marked effects on the bacterial ecology in the intensive care unit with increasing ceftazidime resistance prevalence rates in the respiratory tract and a considerable rebound effect of ceftazidime resistance in the intestinal tract after stopping SDD. However, an alternate explanation was offered for these findings. It was pointed out that in Oostdijk's analysis of resistance all patients, study and nonstudy were included. Abnormal carriage was reported as 5% before, increasing to 15% during and after the trial. However, approximately 70% of the admissions were not actually in the Dutch study conducted by de Smet (31). In contrast, de Smet analyzed surveillance data from only study patients and found the opposite; the proportion of patients with resistant aerobic Gram-negative bacilli to the marker antibiotics, including ceftazidime, was lower with SDD.

A study by Ochoa-Ardila (32) have also recently demonstrated that the long-term use of SDD over a 5-yr period in an adult intensive care unit setting does not increase antibiotic resistance.

SDD using parenteral cefotaxime, enteral amphotericin B, polymyxin, and tobramycin does not cover intrinsically resistant methicillin-resistant *Staphylococcus aureus*. There have been frequent concerns raised about emergence of methicillin-resistant *S. aureus* as a result of using SDD. Enteral vancomycin has been added to the traditional SDD protocol in case of endemicity of methicillin-resistant *S. aureus* (33). There are concerns that enteral vancomycin promotes vancomycin-resistant enterococci (34; however, none of the RCTs and long-term studies using enteral vancomycin have ever reported vancomycin-resistant enterococci outbreaks (35–41). This can be explained by the high fecal vancomycin levels between 3000 and 24,000 mg/L after a 2-g enteral dose. In contrast, studies have shown that 2 g parenteral antibiotic that disregards the human ecology and which are excreted by bile in concentrations <3–95 mg/L of feces promote the emergence of vancomycin-resistant enterococci (42).

Demonstrating an overall survival benefit with SDD may be very hard to achieve in pediatrics because the numbers needed to treat are potentially very large given the low mortality rate in pediatric intensive care. A simple sample size calculation assuming a 5% mortality in the control group looking for a 15% reduction in mortality to 4.25% with a 10% type 1 error or false-positive rate and a 10% type 2 false-negative rate would require a sample size on the order of 27,390 children.

Mechanical ventilation can be seen as a measure of disease severity, defining the need for complex intensive care. The recent Control of Hyperglycemia in Pediatric intensive care trial (CHiP) (43) used as the primary outcome the number of days alive and free from mechanical ventilation within the 30 days after trial entry. The concept of ventilator-free days (VFDs) brings together these two outcomes. A study by Schoenfeld et al (44) define VFDs as: VFD = 0 if the child dies before 30 days; VDF = (30–x) if the child is successfully weaned from ventilator within 30 days (where x is the number of days on the ventilator); or VFD = 0 if the child is ventilated for ≥30 days. The use of organ failure free days to determine patient-related morbidity surrogate end points in pediatric trials has been supported by influential pediatric trialists in the current low mortality pediatric critical care environment (45). Even for this surrogate marker, 1500 children were needed just to be adequately powered to demonstrate a difference of two VFDs. Death was considered an important outcome, but the study was not powered to detect a difference in mortality.

Extrapolating from adult data into pediatric practice is generally considered inadvisable. However, even if the significant reduction in mortality in adults given SDD is to be ignored, the reduction in pneumonia, which parallels the adult observations, tantalizingly hints at the possibility of a potential reduction in mortality in pediatrics, if studies were to be carried out, which were powered adequately with a large enough total number of children. Until this happens, the potential benefit of a proven maneuver in adults is lost to the pediatric world rendering the pediatric population again therapeutic orphans. It took almost 6 yrs from the early suggestions of using of inhaled nitric oxide (46) until a number of RCTs characterized its benefits (47, 48).

Although disparate and small, the four limited studies performed in children allow a meta-analysis, which demonstrates a significant reduction in pneumonia rates. SDD significantly reduces the number of children who develop pneumonia. The study by Barret et al (20) could not demonstrate any treatment benefit from SDD in children with severe burns so at this stage, SDD cannot be advocated in this patient population. Furthermore, there was no overall reduction in mortality nor a reduction in overall infection rates, probably because of the small sample size.

However, on the evidence presented, is it not at least worth considering the use of SDD in certain groups of vulnerable children such as those with a high risk of mortality score or those undergoing solid organ transplantation while awaiting evidence of any survival benefit from large multicentered RCTs?

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LETTERS

MANAGING PERIOPERATIVE RISK

Selective decontamination of the digestive tract may reduce perioperative risk in elective surgery

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Pearse and colleagues review numerous medical interventions for their potential in reducing perioperative morbidity and mortality, all of which they admit lack serious evidence base.[1] Surprisingly, they did not review selective decontamination of the digestive tract, an effective evidence based prophylaxis against pneumonia in patients requiring treatment in intensive care.

Selective decontamination of the digestive tract is well established and has been assessed in 65 randomised controlled trials and 12 meta-analyses including around 15 000 patients.[2] It is an essential component of critical care for patients undergoing major non-cardiac surgery as it improves survival by preventing pneumonia.[3] Patients may also derive as much diagnostic benefit from preoperative surveillance cultures of throat and rectum as from cardiopulmonary exercise testing, discussed in detail by Pearse and colleagues. If surveillance samples give positive results for abnormal micro-organisms, such as aerobic Gram negative bacilli, selective decontamination of the digestive tract should be started preoperatively.[4]

Pearse and colleagues recommend admission to intensive care as part of the multimodal approach to elective perioperative care to improve survival. Therefore selective decontamination of the digestive tract must be included.

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Worlds Apart: Proof that SDD Works

We read with interest Wunderink's editorial "Welkommen to our world" (1) accompanying Oostdijk and colleagues' analysis of resistance patterns during selective digestive decontamination (SDD) (2) in the multicenter randomized controlled trial (RCT) by de Smet and coworkers (3). We disagree with Wunderink that SDD leads to antibiotic resistance. Rather we interpret the original RCT (3) and subsequent analysis (2) as providing strong evidence that SDD reduces infection and mortality without causing the resistance reported.

Resistance can be caused by three mechanisms: (*1*) import, (*2*) acquisition from transmission, or (*3*) *de novo* development (4). de Smet and colleagues' RCT of SDD focuses on bacterial acquisition and *de novo* development in individual patients using surveillance samples. Oostdijk and coworkers analyzed abnormal carriage of aerobic gram-negative bacilli (AGNB) producing extended spectrum β-lactamse (ESBL) at import and point prevalence on the ICU once a month. All patients, study and nonstudy, were included; about 70% of admissions were not actually in the Dutch study (2). Abnormal carriage was 5% before, increasing to 15% during and after the trial. In contrast, de Smet and colleagues analyzed surveillance data from only study patients and found the opposite: the proportion of patients with resistant AGNB to the marker antibiotics, including ceftazidime, was lower with SDD.

Homogeneity in antibiotic prescription is a recognized cause of ecology shift with increased resistance (5). A balanced use of antimicrobials with heterogeneity or diversity reduces the selective pressure that aids development of resistance. The study by Oostdijk and coworkers reaffirms that blanket use of homogenous antibiotics (i.e., SDD with cefotaxime) will result in a shift in unit ecology toward increased cefotaxime-resistant AGNBs. However, Wunderink erroneously concludes that this increased use of cephalosporin leads to increased resistance. This causal link has not been established, is conjecture, and can only be proven with a proper control group.

The ecology in intensive care changes continuously under the influence of many factors, involving patients, staff, and other antibiotics (6), so to attribute the development of ESBL to SDD alone is not good science.

SDD using cefotaxime does result in an ecological shift toward a higher abnormal carriage rate of resistant AGNB. However, using surveillance samples, the evidence clearly shows that it also prevents transmission and *de novo* development of resistance because of the actions of polymyxin and tobramycin (3). More importantly, for 1 in 12 patients receiving SDD, it also reduces mortality.

There is one good point in Wunderink's editorial: that the study by Oostdijk and colleagues may be an aberration of the original RCT.

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Selective decontamination is not sticky

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Dear Editor-in-Chief,
We read the case discussion by Dr. M. J. Smit et al. [1] reporting accumulation of oral antibiotics as an adverse effect of selective decontamination of the digestive tract. The article disappointed us as it did not describe in detail the composition of the paste or suspension nor did the authors estimate the incidence of their reported SDD side-effect. How can your readers assess what actually caused the observed problem if the constituents of the paste are not reported, in particular the percentage of the sticky compound carboxymethylcellulose (CMC) in the paste.

The eradication of abnormal flora including aerobic Gram-negative bacilli (AGNB) and methicillin-resistant *Staphylococcus aureus* (MRSA) from the oropharynx, i.e. oropharyngeal decontamination, is difficult. In 1981, Gerald Bodey wrote that 'antibiotic prophylaxis was less effective against the flora of the throat, probably because of the short contact of antibiotic with the oral mucosa' [2]. The solution came from the experience in dentistry where pastes and gels are commonly used for their prolonged contact time between salivary micro-organisms and metronidazole mixed with pastes and gels [3]. Stoutenbeek [4] was the first to decontaminate the oropharynx of ventilated patients using orabase paste mixed with 2% of polymyxin E, tobramycin and amphotericin B [4]. At the SDD meeting in Jersey in 1988, Crome recommended a gel containing 3% of CMC rather than a paste preparation for oropharyngeal decontamination, the main reason being that the paste is so adherent to the mucosa that removal is difficult and it has a drying effect on the mucosa [5]. In contrast, the gel has good adhesion to the mucosa with prolonged release of drugs but is easy to use.

We have abandoned the paste and replaced it with a gel. The side effect described by Dr. Smit et al. has never been reported during the use of the 3% CMC gel over 20 years. The higher concentration of the CMC in the paste compared with the gel inhibits proper oral care allowing the patient to swallow residual buccally applied SDD paste sticking around the nasogastric tube in the oesophagus.

Unfortunately, Smit et al. have not described the nasogastric tubes or intravenous cannulae they used nor their enteral feeding policies. We in Amsterdam change plastic devices in every patient every 7 days, and have never experienced 'glued' gastric tubes over the last 20 years during which time 14,000 patients received SDD. We believe that enteral feed is a significant cause of obstruction of the esophagus due to solidification of tube feeding [6].

As the total amount of paste used is too small to create the type of solid mass reported by Smit et al., we suggest that a more credible reason for the obstruction observed is that the amphotericin B suspension reacts with the gastric compounds and leads to the formation of a bezoar-type of mass in the upper gastro-intestinal tract following reflux.

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Systemic Antibiotics Fail to Clear Multidrug-Resistant Klebsiella from a Pediatric ICU*

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Study objectives: **To determine the magnitude of infection rate and antimicrobial resistance in a pediatric ICU (PICU), and to evaluate the efficacy of using broad-spectrum antibiotics.**
Design: **A 3-month, prospective, observational cohort audit.**
Setting: **A 12-bed tertiary, referral PICU.**
Patients or participants: **All children admitted to the PICU for > 72 h.**
Interventions: **Surveillance cultures of throat and rectum on admission and once weekly thereafter.**
Measurements and results: **Of the 150 admissions during the 3-month period, a total of 52 patients (24 girls and 28 boys) requiring mechanical ventilation for a minimum of 3 days were enrolled in the audit. The median age and interquartile range (IQR) was 17 months (IQR, 5.8 to 63); length of stay, 6.5 days (IQR, 4 to 13); ventilation days, 5 (IQR, 3 to 11); pediatric risk of mortality score, 14 (IQR, 9 to 19); and risk of mortality, 0.03 (IQR, 0.014 to 0.087). Fifteen patients (29%) developed 21 infections, mainly lower-airway infections and septicemias. Of the 52 children, 7 children carried multidrug-resistant bacteria and 3 patients progressed to develop four infections with those resistant bacteria. Of the seven carriers, six patients carried gentamicin-resistant Klebsiella. Methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and gentamicin-resistant *Pseudomonas aeruginosa* each were carried by one child. Six of those nine resistant isolates were present in the admission flora. Despite the potent combination of piperacillin/tazobactam and amikacin, three children acquired the multidrug-resistant Klebsiella while in the PICU and became nosocomial carriers.**
Conclusions: **Only surveillance cultures allow the distinction between import of multidrug-resistance and resistant bacteria acquired while in PICU. In this study, two thirds of the resistant isolates were imported. The introduction of newer potent systemic antibiotic combinations failed to control the endemic reservoir of multidrug-resistant Klebsiella and suggests that such policies have little impact.**
(CHEST 2001; 119:862–866)

Key words: antibiotic resistance; carriage; gentamicin; nosocomial infection; pediatric ICU

Abbreviations: IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; PICU = pediatric ICU; PPM = potentially pathogenic microorganisms; PRISM = pediatric risk of mortality

In 1992, a hospital-wide outbreak of a multidrug-resistant Klebsiella occurred in our institution. Traditional measures were implemented to clear this endemic strain.[1] These included re-enforcement of strict attention to hand washing, isolation, and introduction of a potent antibiotic combination of piperacillin/tazobactam and amikacin as a first-line therapy to cover the endemic resistant strain. To evaluate the efficacy of using these broad-spectrum antibiotics, a 3-month prospective, observational cohort audit was carried out to determine the magnitude of both infection rate and antimicrobial resistance in our pediatric ICU (PICU).

Materials and Methods

All patients requiring mechanical ventilation for at least 3 days were enrolled in this prospective audit between September 1,

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1997, and November 11, 1997. Age, sex, diagnosis, length of stay, and duration of ventilation were recorded. Severity of illness was quantitated using the pediatric risk of mortality (PRISM) score.[2] The onset of both imported and nosocomial infections was recorded. The first-line antibiotic policy consisted of piperacillin/tazobactam and amikacin. This combination was started on suspicion of infection. Therapy was adjusted depending on microbiological results.

The end points of this audit were to quantitate the overall infection rate and the nosocomial infection rate. The traditional time cutoff of 48 h was compared with the criterion of the carrier state as defined below. We also quantitated the carriage and infection rate of multidrug-resistant microorganisms.

Infection was defined in this study as a microbiologically proven clinical diagnosis of local and or generalized inflammation. This necessitated having a diagnostic sample with the highest growth density from the specimen using the three-segment technique as defined below. In addition, a minimum of a moderate number of leukocytes was required, on a semiquantitative scale of + = few, ++ = moderate, +++ = many leukocytes.

Carriage of resistant microorganism was defined in this study as the isolation from throat and/or gut of a gentamicin-resistant, aerobic Gram-negative bacillus, methicillin-resistant *Staphylococcus aureus* (MRSA), or penicillin-resistant *Streptococcus pneumoniae*.

Diagnostic samples of tracheal aspirate, blood, urine, and pus were obtained on clinical indication only. Diagnostic samples were processed using standard microbiological techniques.[3] The growth density of potentially pathogenic microorganisms (PPMs) isolated from diagnostic samples was estimated using the three-segment technique: low (1+), moderate (2+), and high (3+). Colonies were pure cultured and identified using standard techniques. Isolates were tested for susceptibility to appropriate ranges of antibiotics by disk diffusion using the rotation Stokes technique.

Surveillance samples of throat (swab) and gut (fecal specimen) were taken on admission and thereafter once weekly on Wednesday.[4] The aim of this surveillance program was to distinguish PPM carried by patients on entry to the PICU ("import") from PPM acquired and subsequently carried during their PICU stay ("nosocomial"). Each fecal specimen was screened for antibiotic-resistant microorganisms by incubation overnight at 37°C on MacConkey agar, onto which 8 mg/L of gentamicin discs were put.[5]

The organisms were identified by antibiotyping, using extended-sensitivity patterns (enterobacteria), phage- (*S aureus*), sero- (*S pneumoniae*) and pyocine- (*Pseudomonas aeruginosa*) typing.

Nosocomial or PICU-acquired infection was defined as an infection episode occurring > 48 h after admission to PICU.[6] The carrier-state criterion allows us to distinguish the endogenous infection, *ie*, preceded by carriage from the exogenous infection due to a microorganism not carried by the patient at all.[7] A primary endogenous infection is an infection caused by PPM imported by the patient into the PICU in the admission flora, while a secondary endogenous infection is due to an ICU-associated PPM, not carried on admission but acquired in the unit, followed by carriage and subsequent superinfection. Only exogenous and secondary endogenous infections are "true" nosocomial infections according to the carrier-state criterion.[8]

Results

Of 150 admissions during the 3-month period, a total of 52 patients received mechanical ventilation for > 3 days. The data from this group were analyzed. The demographics are given in Table 1. In this at-risk group, 15 of 52 patients (29%) developed a total of 21 infectious episodes (Table 2). These infections occurred at a median of 4 days (interquartile [IQR] range, 1 to 28 days). Ten of the infections involved the lower airways, and 7 were from blood cultures. Community bacteria including *S pneumoniae*, *H influenzae*, and *S aureus* caused seven infections, particularly of the lower airways. Another seven infections were due to hospital bacteria, including *Enterobacter cloacae*, *Proteus mirabilis*, and *P aeruginosa*. Four infections were caused by multidrug-resistant microorganisms. Gentamicin-resistant Klebsiella was responsible for one case of pneumonia and one case of septicemia at day 16 and day 28, respectively. MRSA caused one wound infection and one case of pneumonia in the same patient at day 2 and day 22, respectively.

Table 1—*Demographics of At-Risk Group*

Variables	Median	IQR
Age, mo	17	5.8–63
Sex, male/female	24/28	
Length of stay, d	6.5	4–13
Duration of ventilation, d	5	3–11
PRISM score	14	9–19
Risk of mortality	0.03	0.014–0.087

Of 52 patients, 7 patients carried a multidrug-resistant PPM; 3 patients developed four infections due to those multidrug-resistant PPMs (Table 3). The carriage profile of the seven patients included gentamicin-resistant Klebsiella carried by six of seven patients, MRSA in one of seven patients, penicillin-resistant *S pneumoniae* in one of seven patients, and gentamicin-resistant *P aeruginosa* in one of seven patients. Six of these nine resistant strains were imported by the patient into the unit. Nosocomial carriage occurred in three children and was invariably due to gentamicin-resistant Klebsiella. Those three cases of nosocomial carriage reflected the transmission rate in the PICU. In obtaining surveillance samples, there was a 80% compliance rate for the first sample and 70% for the second sample.

Discussion

Although there were 150 admissions to our unit during this study, we were more interested in those who required mechanical ventilation for > 3 days. Thus, we focused on analyzing 52 patients. We feel this group reflects our sickest patients and those at greatest risk of nosocomial carriage and infection.

Table 2—*Details of Infections and Carriage of Similar Microorganisms

Patient No.	Infection Site	ICU Day	Organism	Import Carriage	Nosocomial Carriage†	Pathogenesis
1	Lower airways	2	*S aureus*	*S aureus*		Primary endogenous
2	Lower airways	2	*P aeruginosa*	*P aeruginosa*		Primary endogenous
	Septicemia	3	*P mirabilis*	*P mirabilis*		Primary endogenous
3	Digestive tract	10	*Ascaris lumbricoides*	*Ascaris lumbricoides*		Primary endogenous
4	Lower airways	2	*Haemophilus influenzae*	*Haemophilus influenzae*		Primary endogenous
5	Lower airways	6	*S aureus*	*S aureus*		Primary endogenous
	Septicemia	7	CNS	Not investigated		
	Lower airways	16	Klebsiella (gentamicin resistant)	Klebsiella (gentamicin resistant)		Primary endogenous
6	Lower airways	2	*H influenzae*	*H influenzae*		Primary endogenous
7	Septicemia	1	CNS	Not investigated		
8	Stomatitis	4	*Candida albicans*	*Candida albicans*		Primary endogenous
9	Gastrostomy wound	2	MRSA	MRSA		Primary endogenous
	Neck wound	5	*P aeruginosa*	Negative		Exogenous
	Lower airways	22	MRSA	MRSA		Primary endogenous
10	Septicemia	22	CNS	Not investigated		
	Septicemia	22	*P aeruginosa*/CNS	Negative	20	Secondary endogenous
11	Lower airways	3	*E cloacae*	*E cloacae*		Primary endogenous
12	Septicemia	7	*C albicans*/CNS	*C albicans*		Primary endogenous
13	Septicemia	28	Klebsiella (gentamicin resistant)/*Escherichia coli*	Negative	26	Secondary endogenous
14	Lower airways	2	*S pneumoniae*	*S pneumoniae*		Primary endogenous
15	Lower airways	2	*S aureus*	*S aureus*		Primary endogenous

*All but three CNS infections were evaluable for analysis by the carrier-state criterion. Eighty-five percent (15 of 18) of infections were of primary endogenous development, while only 3 infections, 2 of secondary endogenous and 1 of exogenous pathogenesis, were true nosocomial infections and due to microorganisms acquired in the unit.

†Nosocomial carriage = ICU day on which the microorganism was detected by surveillance culture.

The use of a population size of 150 as a denominator would minimize the problem and would not allow any room for improvement.

Three findings emerged from this study. Firstly, the overall infection rate in the sickest patients was 29%. Using the traditional 48-h cutoff, nosocomial infection occurred in 17.3% of patients (9 of 52); therefore, it would appear that 61% (15 of 21) of all infectious episodes were due to microorganisms acquired on the PICU. Using the criterion of the carrier state, nosocomial infection occurred in 6% (3 of 53) and 15% (3 of 21) of all infections were caused by nosocomial PICU microorganisms.

Table 3—*Carriage and Subsequent Infections Due to Resistant Microorganisms*

Microorganisms/ Patient	Carriage	Infection
Gentamicin-resistant Klebsiella		
Patient 5	Import	Lower airways
Patient 9	Nosocomial	—
Patient 13	Nosocomial	Septicemia
Patient 14	Nosocomial	—
Patient A*	Import	—
Patient B*	Import	—
MRSA		
Patient 9	Import	Wound: gastrostomy, Lower airways
Penicillin-resistant *S pneumoniae*		
Patient C*	Import	—
Gentamicin-resistant *P aeruginosa*		
Patient 9	Import	—

* Patients A, B and C were only carriers, with no evidence of infection.

Secondly, of the 52 children studied, 7 children carried resistant strains that were imported by four patients. Therefore, three children acquired the resistant strains during their PICU stay, suggesting transmission via hands.

Thirdly, despite using the combination of piperacillin/tazobactam and amikacin in all 52 children, it was only justified in 3 patients who carried the gentamicin-resistant Klebsiella on admission. Thus this potent antibiotic combination failed to prevent transmission, acquisition, and carriage to these three children, one of whom went on to develop a secondary endogenous Klebsiella infection.

Our nosocomial infection rate of 17.3% is comparable to rates reported by other PICUs.[9–11] There is consensus that the single most important factor responsible for infection in PICU is illness severity and related immunoparalysis.[12,13] This figure of 17.3%, using the 48-h cutoff, was identified in a subset of children with a median PRISM score of 14, and who required a median stay of 6.5 days and 5

days of ventilation. The nosocomial infection incidence was 5%, and 15% of all infections were due to PICU microorganisms, according to the carriage criterion. We prefer the carrier-state classification, because this concept enables us to usefully reclassify a substantial number of infections considered traditionally to be PICU acquired into the imported group. Thus, based on our carrier-state classification, we transferred nine infections (50%) from the traditional nosocomial group to the import group. By identifying the 85% of all infections imported by the patients in their admission flora, we could accurately detect the 15% of true nosocomial infections, revealing the magnitude of the cross-infection problem due to transmission. The two major advantages of the carriage criterion are as follows: first, the population with primary endogenous infections can be identified, thereby explaining all infections after 48 h; second, knowledge of carriage on admission and throughout the PICU stay prevents fruitless investigation of apparent cross-infection episodes. Finally, without surveillance samples, exogenous infection,[7,14] which can occur at any time due to breaches of hygiene, are impossible to recognize at least at an early stage, when only diagnostic samples such as tracheal aspirate, urine, and blood have been tested.

Resistant PPMs were carried by 13.5% of all patients studied. Surveillance samples of throat and gut revealed that > 50% of the children imported the resistant strain onto the PICU. Our findings are similar to those of two studies[15,16] that examined the carrier state of resistant PPM in pediatric patients. In those two studies, respectively, 30% and 50% of patients carrying resistant PPM were detected within 24 h of admission, using surveillance techniques. In our study, four different resistant strains—penicillin-resistant *S pneumoniae*, MRSA, gentamicin-resistant *P aeruginosa*, and Klebsiella—were detected in the 52 patients over 3 months. Surprisingly, transmission of only the resistant Klebsiella occurred. Three children acquired and subsequently developed the secondary carrier state of resistant Klebsiella. One child (patient 13 in Table 2) developed secondary endogenous septicemia with the nosocomial Klebsiella strain.

The knowledge of carriage of resistant microorganisms both imported and acquired is beneficial for the individual patient. A patient who only carries normal flora and does not carry opportunistic resistant PPMs in throat and gut is at low risk of infection.[16–18] This type of patient does not require new potent and expensive antimicrobials such as β-lactams, combined with β-lactamase inhibitors, fluoroquinolones, and carbapenems. In this study, all children received "blind" therapy with piperacillin/tazobactam and amikacin. Surveillance cultures showed that this blind combination was justified in three children only, who carried the resistant Klebsiella strain on admission to the PICU. But more important, the particular systemic antibiotic combination used failed to prevent the development of carriage of the resistant Klebsiella in three children who required long-term mechanical ventilation. Our study suggests that a strict antibiotic policy using a potent parenteral antibiotic combination does not influence the carrier state of resistant PPM, both imported and subsequently acquired. This important observation may be explained by the fact that systemic antibiotics only rarely reach lethal salivary and fecal concentrations following excretion via saliva, bile, and mucus into throat and gut. Most parenteral antibiotics fail to clear carriage of resistant PPM.[19] Our experience is consistent with data[20] from Cleveland Children's Hospital, where the introduction of a identical antibiotic policy failed to reduce a similar resistance problem. To decrease the reservoir of carriers of resistant strains in the PICU, antibiotic policies will need to be coupled with other strategies. Routine surveillance samples on the subset of long-stay children together with oral nonabsorbable antimicrobials as the most important part of selective digestive decontamination will likely be necessary components of this effort,[21] barrier precautions being an example.[22] Adjustment of blind therapy at an early stage is only possible if the surveillance cultures are an integral part of the infection control policy. Selective digestive decontamination using oral nonabsorbable antibiotics polymyxin E and tobramycin has been shown to be very effective in prevention and, if present on admission, eradication of the abnormal carrier state of resistant Klebsiella.[21,23–26]

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Should morbidity replace mortality as an endpoint for clinical trials in intensive care?

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Intensive care medicine has recently seen the rejection of several promising new treatments: monoclonal antibodies to endotoxin, to tumour necrosis factor, and to cytokine modulators such as interleukin-1 receptor antagonist were developed, tested, and rejected within the space of a few years on the grounds that they did not lessen mortality. [1] But was this ever a realistic objective?

Mediator-directed measures are not the only forms of intensive care unit (ICU) treatment to fail this litmus test of ICU-based clinical trials. Indeed there are few, if any, interventions currently in use in the ICU that have been demonstrated unequivocally to reduce mortality, and ICU mortality rates have remained unchanged at 30–50% over the past 30 years.[2] ICU funding accounts for up to 20% of inpatient hospital costs[3] and the financial impact of interventions that lack efficacy will be considerable. However, we risk discarding treatments that may by other criteria prove beneficial.

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Is a reduction in ICU mortality achievable?

Why do ICU patients die? Do they die of an inability to control overwhelming infection or do they die because of an overactive host response? Do they die because treatment cannot support failing organ function or because the act of supporting the failing organ causes further injury? Or do they die because we decide we can go no further and limit or withdraw support. If we know the cause of death for a particular condition and if treatment alters the pathological process leading to death, then mortality is an appropriate study endpoint. However, it is unproven that patients die because of an inadequate antibody response to aerobic gram-negative bacilli or because of overproduction of tumour necrosis factor or interleukin-1. Thus we should not assume that an intervention which targets these will lead to a reduction in ICU mortality.

Mortality is a useful endpoint to evaluate the pathophysiological mechanism of disease in animal models[4] and such studies can provide insights relevant to management of human disease; for example, demonstration that the effects of manipulation of a cytokine such as interleukin-10 can be diametrically opposite depending on the model used[5] has raised the possibility that attempts to completely antagonise the cytokine response to sepsis may inappropriately switch off defence mechanism of benefit in the containment of

infection. But it is a naive leap of faith to assume that a single intervention that can alter mortality in the controlled and homogeneous context of an animal study will have a similar benefit in the clinical arena where the diseases to be treated are complex, patients are heterogeneous, and the nature of the threat to survival is ill-defined.

Even if the disease process is so well characterised that response to treatment can reliably be predicted, large sample sizes are needed to show a reduction in mortality. The use of mortality as an endpoint assumes a homogeneous patient population. ICU patients, even those with defined physiological abnormalities such as sepsis syndrome, do not comprise such a homogeneous group. Moreover, even in studies of myocardial infarction where populations are homogeneous and the relation between intervention and mortality is clear, large sample sizes are required to show statistical significance. Lau calculated that, for a treatment that reduced mortality due to myocardial infarction by 5%, 10 000 patients were needed to show a statistically significant effect.[6] The small number of patients admitted to an ICU does not permit trials of this magnitude.

Large sample sizes in ICU-based trials are required, in part, because for a given diagnosis patients face a spectrum of risk based on the severity of physiological derangement at the time treatment is started.[7] Some patients will improve irrespective of treatment while others will die despite effective treatment: the cohort of patients in an intermediate risk range, where therapeutic benefit might be seen, is substantially smaller than the total patient population.

What manoeuvres currently used in ICUs have actually been shown to improve survival? Ventilation is obviously life saving in apnoea, although no particular mode of ventilation has been proved to reduce overall ICU mortality. Total parenteral nutrition may prolong life for patients with short-gut syndrome, but its role in critical illness is undefined. A review of 5 randomised studies, involving 500 patients, concerning the effect of enteral nutrition versus parenteral feeding on infection suggests advantages for early enteral feeding. Neither mode seemed to alter mortality.[8] Inotrope support is a mainstay of ICU care. A prospective study of dobutamine in adequately hydrated patients was abandoned as survival in the treatment group was actually lower.[9] No controlled trial has demonstrated improved clinical outcome associated with low-dose dopamine for renal protection.[10] The annual costs of pulmonary artery flotation catheters in the USA approach 2 billion dollars,[11] yet this device has never been shown to improve overall survival. Nor have infection control methods such as hand washing and mask wearing been proved to alter mortality although they may reduce infection transmission.[12]

The lack of a demonstrable effect on mortality does not signify that a treatment is worthless and we are concerned that potentially useful interventions may be abandoned because of the limitations of trial methodology. Although corticosteroids failed to improve survival in a heterogeneous group of ICU patients with sepsis syndrome,[13] we know that high-dose dexamethasone is beneficial in chloramphenicol-treated patients with severe *Salmonella typhi* septicaemia.[14] Similarly, it is possible that monoclonal antibodies and cytokine modulators will prove useful in certain patient subsets, or in combined therapy. Antibodies to TNF can moderate the inflammatory response in Crohn's disease[15] and may reduce pyrexial swings in malaria.[16]

The current standard endpoint for ICU-based clinical trials is 28-day all-cause mortality. Patients who die later are considered treatment successes, even if their death is directly related to the disease treated in the ICU. Conversely, critically ill patients may die early because of intercurrent conditions unrelated to their primary illness. Estimation of cause-specific mortality introduces potential for bias and will fail to detect mortality related to the adverse effects of treatment. Survival curves provide useful information on the effects of treatment, but is prolonged survival desirable if the patient will never leave the ICU? For patients who eventually return to an independent existence, the duration of their subsequent survival may be little affected by treatment received during the ICU stay.

Reducing morbidity: an achievable endpoint

If overall ICU mortality has remained the same for 30 years and if new treatments have not reduced mortality, should we not shift our focus to reducing morbidity? Disease-specific measures of quality of life are increasingly used in disease processes such as rheumatoid arthritis[17] or inflammatory bowel disease[18] for which mortality is clearly an inappropriate endpoint. In the ICU setting, measures reflecting ICU-specific morbidity such as severity of multiple organ dysfunction syndrome, nosocomial infection, and length of stay are more relevant endpoints.

A reduction of morbidity is an accepted endpoint in many other realms of investigation. Antimicrobial prophylaxis given before colon surgery for carcinoma reduces postoperative infection rates from 30% to less than 10%.[19] Survival benefit has never been the primary endpoint of this prophylaxis; indeed overall mortality from colon carcinoma has not changed. Similarly, endocarditis prophylaxis is designed to avoid valvular damage and reduce morbidity[20] but has not reduced overall death rates.

In measuring morbidity we are interested in measures that either improve the quality of life or reduce costs. Reduction in haemodynamic and respiratory instability during ICU admission will lessen morbidity. The prevention of pneumonia or systemic inflammatory response avoids the need for increased ventilation pressures, reduces the risk of barotrauma and oxygen toxicity, and shortens the time to extubation. Although subject to a great deal of variation from one unit to the next, and influenced by extraneous pressures such as the availability of ward beds, length of stay is a useful measure of both ICU morbidity and ICU costs. Overall morbidity may be measurable with an aggregate variable such as an organ dysfunction score. Similarly, analyses based on the costs of therapy may prove more relevant in decision making.[21]

It has been suggested that as few as 15% of medical interventions have been adequately validated.[22] In a setting where the potential to do harm and generate unnecessary costs is exceptionally high, intensive care physicians have a responsibility to question dogma. Regulatory agencies such as the USA Food and Drug Administration have recently begun to doubt the primacy of all-cause mortality as an endpoint for ICU-based clinical trial (Roberts R. Letter to participants at the roundtable symposium on the design of clinical trial in sepsis). Intensive care physicians should be taking the

initiative in developing and validating more appropriate instruments to determine the efficacy of our interventions.

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BOOKSHELF

Raising Lazarus

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Raising Lazarus is the story of Robert Pensack's nearly life-long struggle with a mortal illness, idiopathic hypertrophic subaortic stenosis (IHSS). The author, a psychiatrist in Colorado, collaborated with the writer Dwight Williams to produce this remarkable and often disturbing story of Pensack's battle with his flawed heart. Pensack's medical history is typical for IHSS patients, but his personal story is written through the lens of a physician, imparting a unique perspective of physician-author as patient. The main theme explored in *Raising Lazarus* is that facing a chronic and potentially fatal illness is a personal war, complete with the horrors of battle and the ever-present risk of defeat, as well as the occasional taste of victory.

The author's battle with his illness begins at the age of 4 when his mother dies of IHSS. Pensack and his older brother inherit from her the mutated gene that will doom them to heart failure at an early age. By age 17 the author is experiencing palpitations and syncope and begins to suffer the anxiety and depression that will plague him relentlessly. Fascinated by his genetic illness, he enters medical school, in part to learn more about the process already weakening his myocardium. As a medical student he becomes elated that self-knowledge of his own condition "is evidence that I can master this disease, come to know it so intimately that I will be able to survive with it. I am a spy in the house of my heart". But his medical studies are soon interrupted by congestive heart failure, and he travels to the National Institutes of Health in Maryland for an attempt at corrective surgery. During recovery from his open heart operation, Pensack suffers a cardiac arrest. He undergoes a typical out-of-body experience, floating up and away from his body, able to look down calmly at himself on the bed, his cardiologist working frantically to restore a heartbeat. As he observes his own near death, the 25-year-old patient accepts for the first time that he is slowly dying. As he awakens from this brush with death, he perceives a new reality "the unbearable terror of this world, the immense burden of being alive".

After he recovers from surgery and re-enters medical school, the author considers a career in surgery—perhaps another effort to gain control of his illness. However, the rigours of a surgical internship are more than his heart can bear, and he decides to train in psychiatry. But even this less physically demanding specialty becomes too much for him, and Pensack is compelled to face the ultimate terror—a heart transplant. Cardiac transplantation at age 42 is the major battle in Pensack's private war, and although he ultimately survives, the cost is high. He suffers enormous anxiety during the long wait for a suitable donor, and is reduced to combing the television channels for news of a young accident or suicide victim whose heart might become his. The 13-hour operation is described in harrowing detail by Dwight Williams, who met Pensack before the operation and who witnessed the transplant. During the prolonged recovery Pensack's enormous physical discomfort and constant fear of death are compounded by a deepening guilt that his survival was possible only because the donor's accidental death made a heart available.

Raising Lazarus, as the title implies, is about the conquest of death and return to life. On a deeper level the book explores the frightening dilemma that doctors face when